Volume XXI Number 5

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DISEASES OF THE NERVOUS SYSTEM

A Practical Journal on Psychiatry and Neurology

MAY
1960

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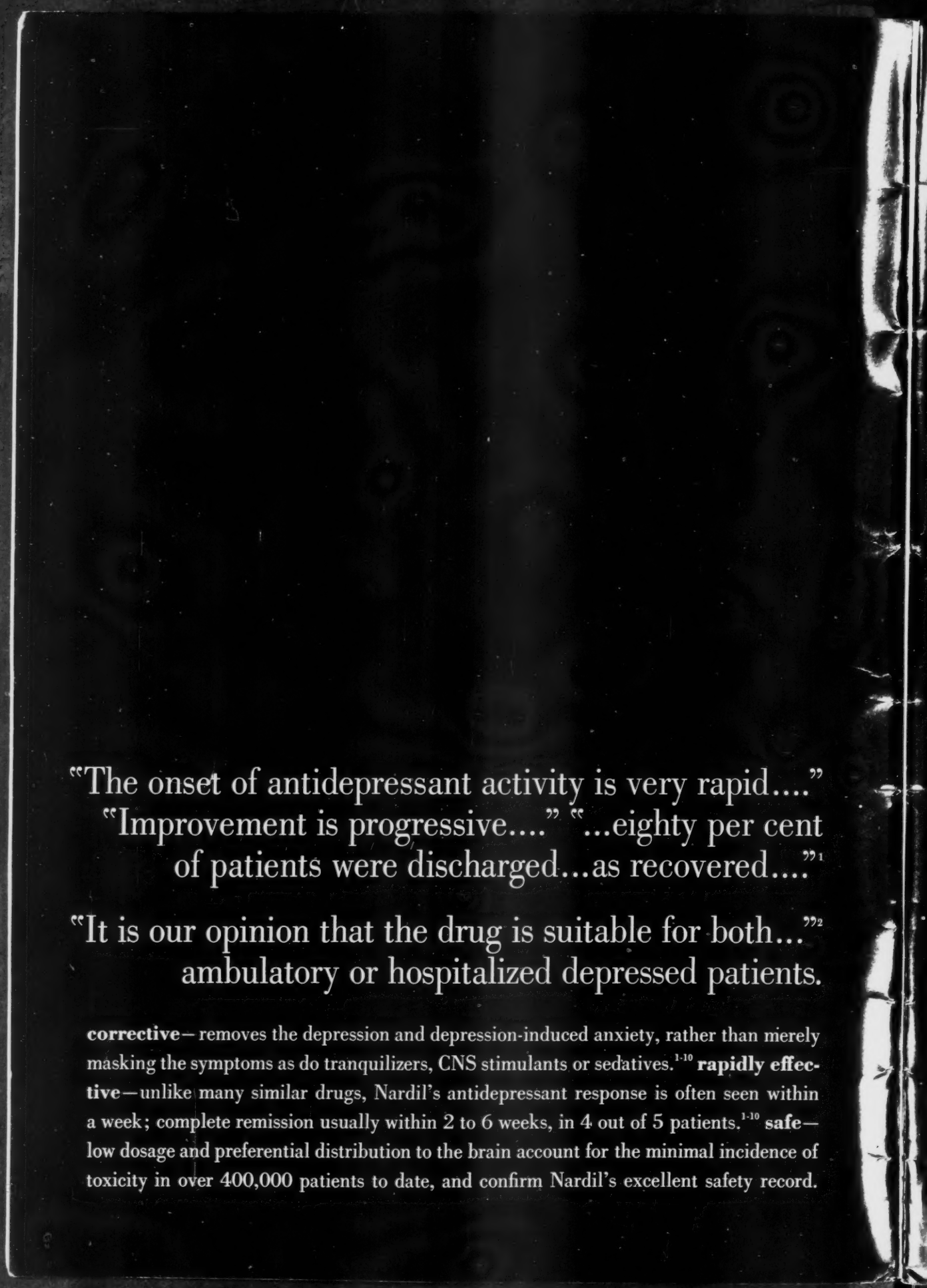
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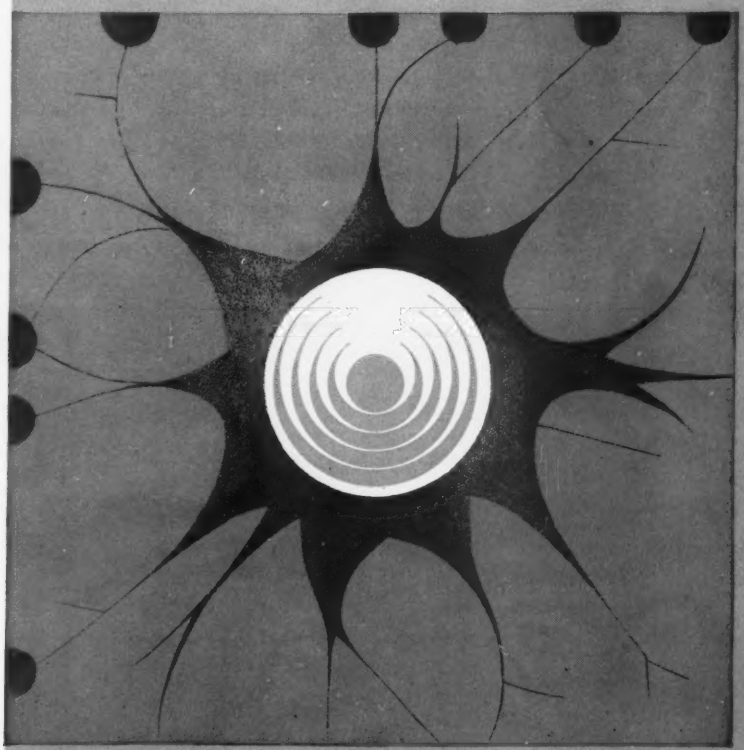

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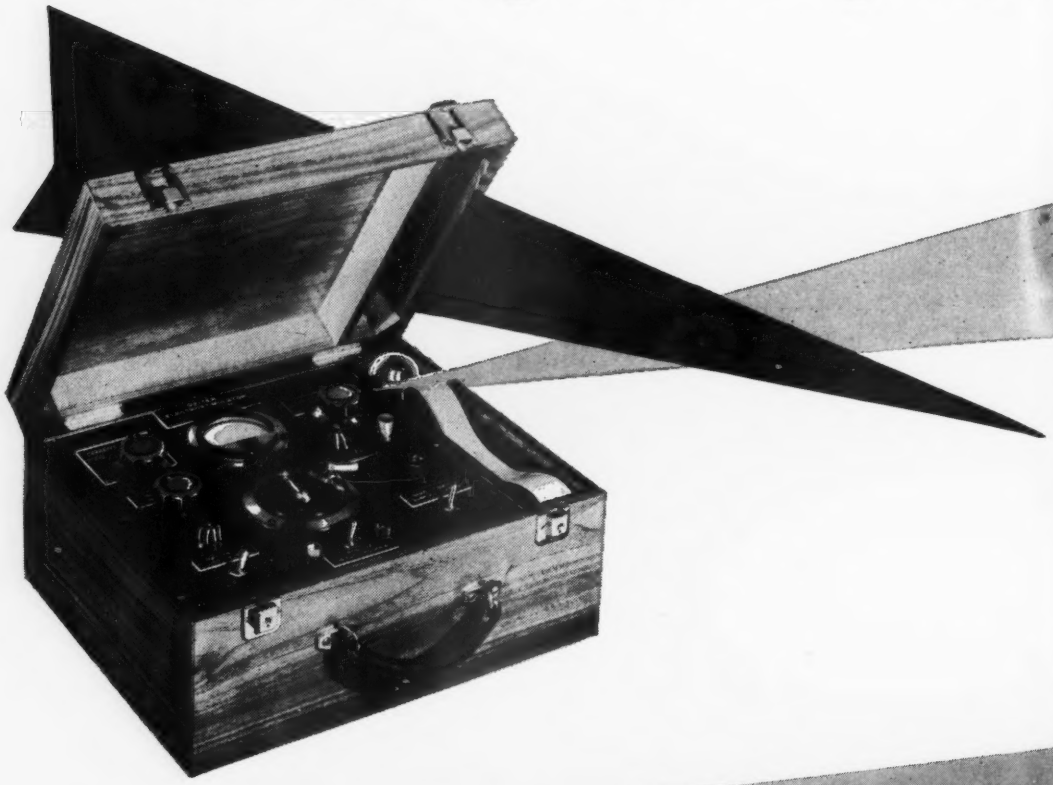

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Volume XXI MAY 1960 Number 5

DISEASES *of the* Nervous System

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Fungus Infections of the Central Nervous System

(Current Status of Management)

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LOUIS D. BOSHES, M.D.

Until recently, fungi and molds were hardly considered causes of disease and were usually pictured as harmless inhabitants of dark cellars, stale bread or exotic cheeses. The most familiar is the mushroom, but the more valuable are the numerous varieties of fungi from which a whole family of life-saving antibiotics, including penicillin, terramycin, streptomycin, aureomycin, achromycin, chloromycetin and dozens of others have been derived. While some varieties of these fungi have saved many lives, others are of a malign nature and have infected, or even killed, an equal number.

Fungus infections in man, until recently, were not considered serious involvements but this premise is no longer valid. We do not have accurate vital statistics on fatalities from fungus infections inasmuch as this cause of death is rarely recorded. However, in 1951 the United States Vital Statistics recorded 338 who had succumbed to systemic fungus diseases. Of those who do not die, many become disabled with the residua and the sequela.

Nickerson[1] has postulated that "fungus infections are probably the most widely distributed and most numerous types of infections." Within the past ten years, there has been a resurgence of interest in the treatment of these diseases and numerous medications have appeared in the armamentarium of the physician but until recently, there was very little in the way of any specific management noted. In fact, in 1956, we stated that, "It is apparent that the clinician remains powerless in most instances in the management of fungus infections." This premise is no longer true because at the present time, new effective agents have appeared with most promising results in fungus infections which hitherto have been most resistant to any type of medication. I will discuss the management of the more commonly encountered mycoses which affect the central nervous system. These are actinomycosis, nocardiosis, North and South American blastomycosis, coccidioidomycosis, cryptococcosis, candidiasis, aspergillosis, mucoromycosis, sporotrichosis, maduromycosis, chromoblastomycosis and histoplasmosis.

At the present time it might be stated that there are four so-called "deep" fungus diseases which have specific therapy, namely, actinomycosis, nocardiosis, blastomycosis and coccidioidomycosis. For the others that I have listed, there is as yet no specific treatment but new anti-fungal agents which have appeared recently have changed the picture considerably and numerous cases with clinical bacteriological arrests have been reported. In addition to the specific medications, general therapy directed to all these cases includes bed rest, adequate diet, transfusions, vaccines, steroids, etc.

ACTINOMYCOSIS AND NOCARDIOSIS

Actinomycosis bovis and nocardiosis asteriodes belong in the order actinomycetales and are in an intermediate position between the true bacteria and the other fungi. This fungus has world-wide distribution is more common in rural than in urban zones, and is seen most often in men in the second to fourth decades of life. Actinomycosis of the central nervous system is infrequently seen

From Department of Neurology and Psychiatry, Northwestern University Medical School, Chicago, Illinois, and Division of Neuropsychiatry, Michael Reese Hospital, Chicago, Illinois.

but when infection does occur, a meningitis with or without a brain abscess occurs. Often there are multiple abscesses. Meningitis is most commonly seen in this group. The common types of strains are believed to be actinomycosis israeli for the human and actinomycosis bovis for the bovine species.

Infection of the central nervous system generally follows a primary infection elsewhere in the body. The spread is through the meninges by direct extension from a primary focus in the soft tissues or bony cavities of the head. Generally the jaw is involved but any other portion of the face, mouth, throat, middle ear or nasal sinuses may be involved. The infection may enter the cranium via the foramina at the base of the skull. Central nervous system involvement may result as an invasion of the blood stream through an infection of the lungs, bronchial glands, gastrointestinal tract or even the skin. Once there is generalized septicemia, secondary lesions may result.

Pathology: There may be a varied form of reaction with meningitis most common. The inflammatory exudate in the subarachnoid space may be thick and yellowish and is often composed chiefly of leucocytes, fibroblasts and fungi, which are seen in granules as lobulated bodies composed of delicate branched intertwining filaments. These club-shaped structures are seen in optical sections around the periphery, giving the picture of atypical granules with clubs, hence the name, "ray fungus." These are the gram positive sulfur granules which are present in abscesses and draining sinuses. A brain abscess which may exist with or without a meningitis is another pathologic feature.

Symptomatology: This depends upon the type and location of the pathological involvement. Focal signs or symptoms generally seen with a brain abscess may produce convulsions, hemiparesis with the usual associated reflex changes, and visual disturbances. Other symptoms and findings include headache, dizziness, vomiting, papilledema, meningeal signs, delirium and coma. The fever rarely exceeds 102° F.

Laboratory Findings: The white count may vary between 15,000 to 25,000. The cerebrospinal fluid is usually purulent, yellow and may be so thick that it cannot flow through a spinal puncture needle. The cells may number several hundred per cubic millimeter and are chiefly polymorphs. Total protein generally is increased, chloride content is low, and sugar is absent or decreased. The course is relatively chronic and may extend over a period of months, up to three years, or sudden death may occur.

Treatment: In the past, practically every case of actinomycosis meningitis was fatal. However, combined penicillin and sulfonamide therapy or penicillin-streptomycin combinations, have helped many cases,[3] with dosages of a million units daily for up to two months. Other authorities[4] have used doses of 10 to 20 million units intravenously for as much as 35 days, together with wide surgical excision. Harvey follows up his treatment by using 2-5 million units intravenously for as long as 12 to 18 days. Jacobson and Cloward[5] even used intrathecal penicillin with 50,000 units daily, and 5 grams of the sulfadiazine daily, with complete success and their patient went on to an uneventful recovery. Bates and Cruchshank[6] advocate up to 6 million units of crystalline penicillin daily for six weeks, surgical drainage, and then 600,000 units of penicillin daily on an out-patient level for at least six weeks. They have also advocated the use of iodides, particularly when there is lung involvement since the action of the iodides is resolution of fibrous tissue. Some of the newer drugs, to include tetracycline, erythromycin and chloramphenicol have proven successful in some cases but do not compare with penicillin in efficacy. In summary, then, massive doses of penicillin given early, together with surgical drainage, may result in a 50 per cent recovery rate.

NOCARDIOSIS

Nocardiosis asteroides (Eppinger, 1894) is the most common pathogenic species seen in this country. This is a chronic granulomatous involvement which may affect all viscera including the brain. This organism simulates actinomycosis but lacks the sulfur granules and exudates. Sinus formations are

rarely seen, and in general, the disease process resembles tuberculosis. The organisms are gram positive or partially acid fast delicate intertwining branched hyphae that often break up into bacillary forms.

Treatment: The sulfonamides, including sulfadiazine and sulfamerazine, are the drugs of choice. Peabody and Seabury[7] combine sulfadiazine with streptomycin giving 4-12 grams of sulfadiazine together with 2 grams of streptomycin daily, even though antibiotics have been used initially. Gantricin has been employed regularly. Rankin and Javid[8] at the University of Wisconsin Medical School described a case of nocardiosis of the central nervous system treated successfully with surgical excision following prolonged chemotherapeutic and antibiotic therapy. Emphasis was placed on the importance of sulfadiazine. There are some who believe that antibiotics should be substituted for all sulfonamides.[9]

BLASTOMYCOSIS

North American Type: This mold disease has been reported in various areas of North America but chiefly in the central states of the United States. Most often it affects farmers largely in third to fifth decade of life. How the infection is acquired still remains a mystery. The disease process is characterized by single or multiple granulomatous lesions of the skin and by single or multiple granulomatous lesions in the internal organs. In the systemic form, widespread dissemination of the organism occurs following invasion through the respiratory system. Metastatic lesions may occur anywhere in the body via the blood stream. Infections of the brain and meninges may be preceded by involvement of bone or soft tissue adjacent to central nervous system structure with subsequent direct spread to the nearby nervous tissue.

Pathology: Grossly, the pathologic changes resemble those of tuberculosis and the lesions consist of miliary abscesses containing the blastomycetes, multinucleated giant cells, plasma cells, round cells, and considerable necrotic material. Obviously, the tendency to abscess formation is high. The cerebrospinal fluid may be clear or turbid, with a cell count rarely higher than 500 per cubic millimeter. There may be a preponderance of either polymorphonuclear leucocytes or monocytes. The protein level is usually elevated, the chlorides and sugar diminished. The organism, blastomyces dermatitides, is a single or budding spherical cell, 8-15 u in diameter with thick refractile wall. There are no mycelia present.

Symptomatology: Symptoms are usually chronic and most skin lesions are painless. In the nervous system, signs and symptoms are those of a chronic meningitis lasting weeks, months, or even longer. Focal signs of cranial nerve palsies are seen occasionally. Coma finally appears and the outcome is generally fatal. The diagnosis, then, is made on the discovery of other systemic involvements of the disease, by tissue biopsy and by growing the organism on a suitable culture medium. There is no complement fixation available for this illness.

Treatment: The most accepted treatment, almost specific in many cases, is 2-hydroxystilbamadine. Smith[10] recommends 100 milligrams the first day, 150 milligrams the second day and 225 milligrams the third day. Given in small amounts of saline, the doses are continued daily until a total of 9-12 grams is reached. Potassium iodide, used successfully by Gilchrist in 1894, is still accepted as a reliable form of management and may be curative in some instances. Vaccines and x-ray therapy are still employed as adjunctive measures. Desensitization with vaccines is still employed.[10] Mycostatin, one of the new antibiotics, has been effective. Recently, Gold[11] and others isolated a streptomycete culture possessing antifungal activity from soil in the Orinoco Region of Venezuela. These investigators attributed this activity to two related antibiotics, namely, Amphotericin A and Amphotericin B, which later were isolated in crystalline form by Vandeputte and associates.[12] Amphotenicin B is advised in resistant cases.

South American Type: This is a chronic granulomatous disease of the skin, mucous membranes, lymph nodes and internal or-

gans caused by the blastomyces brasiliensis. This form is distinguished from the dermatitis or Gilchrist type by multiple budding yeast-like forms which are large, spherical and thick-walled. The clinical picture varies little from the North American form. It often resembles tuberculosis and has numerous visceral manifestations plus invasion of the central nervous system. Treatment is similar to that of the North American type.

COCCIDIOIDOMYCOSIS

This disease is endemic in California, Arizona, New Mexico and southwest Texas. It has been reported elsewhere in the United States, Mexico, Argentina, Venezuela and Paraguay. First recognized in 1892, it has continued to mount in importance and during World War II some 6,000 American troops stationed in the southwest area of the United States became infected with this disease and 50 succumbed. Both sexes and all ages are affected. Dark-skinned races seem prone to develop the granulomatous form of the disease. Coccidioidomycosis has been reported in animals. In dogs, strangely enough, it has not been found in any breed except the boxer. It is estimated that 10 to 15 per cent of newly arrived residents in coccidioides areas contract the infection in the first year, with or without obvious symptoms. Synonyms include valley fever, desert fever and San Joaquin fever.

When coccidioidomycosis invades the nervous system, it is the result of a dissemination of infection from a primary site which is nearly always the lung. This illness usually proves fatal. Forbus[13] reported that 10 per cent of patients in his series developed central nervous system involvement confined to the meninges. Schlumberger[14] noted an incidence of 13 cases of basilar meningitis in 23 cases of disseminated coccidioidomycosis studied at the Army Institute of Pathology while Abbott and Cutler[15] reported an incidence of 25 per cent. It should be remembered that the primary point of entry may escape detection at autopsy so that only the central nervous system involvement is obvious.

Pathology: The disease produces a thick fibrous meningeal exudate around the base of the brain, suggesting the clinical picture of meningeal encephalitis or even neoplasm.[16] At times the granuloma may even resemble a spinal cord tumor.[17] The cerebrospinal fluid resembles that seen in tuberculosis meningitis. It may be clear, turbid or anthochromic. The cells may number from 100 to 2500 per cubic millimeter. Protein is elevated while sugar and chloride contents are diminished. In some cases, the organism may be isolated from the fluid. Otherwise, it may be identified in the tissue with P.A.S. stain (periodic acid-Schiff reagent) or the Hotchkiss-McManus technique.[18] At the present time, another technique, the Goman-methenamine silver stain, is also employed to demonstrate the fungi, which is a non-budding, thick-walled structure, 20-80 u in diameter, filled with numerous small 2-3 u endospheres.

Symptomatology: The clinical diagnosis is dependent upon a healthy suspicion and awareness particularly in a case with pulmonary involvement that does not clear up within a reasonable length of time under regular regimen. In most instances, no organism can be identified with the fluid either on smear or culture but only by complement fixation and precipitin studies on the serum and on the spinal fluid. Until recently, death usually occurred within 4-5 years although cases of survival for 10 years, without any specific treatment, are on record.[19]

Treatment: At the present time the most effective drug seems to be Amphotericin B, considered fungicidal if given early and fungostatic if administered later. Klapper et al. have reported an apparent cure, after treatment with Amphotericin B, of a patient with widespread coccidioidomycosis of some 10 years' duration. The drug was well tolerated over a period of 14 months. Mycostatin was also used as adjunctive treatment. Litman, Horowitz and Swade[21] have used Amphotericin B, reporting encouraging results. They even resorted to intrathecal injections. Aminostilbamidine has been tried in many instances but has been shown to be completely ineffective.[2,22] Jenkins and Postlewaite[16] employed Actidione, the antibiotic cyclohexamide, in two cases of this

fungus involvement. One of the cases survived. Arsphenamine crystals, gentian violet, thymol, and other related oils are still employed as therapy. Most of the newer antibiotics have failed in the treatment of disseminated coccidioidomycosis of the central nervous system.

CRYPTOCOCCOSIS

Cryptococcosis is an infection caused by the cryptococcosis neoformans, the only yeast known to infect and kill animal and man. Known also as torulosis and European blastomycosis, it was first described as a human disease in 1911. It occurs in all areas of the world and affects both sexes and all ages. The organism is probably widely disseminated in the soil where it leads a harmless life. Pasteurization kills the organism in course. The number of cases discovered is mounting gradually as familiarity with this disease increases.

Pathology: A complete pathological picture of this disease complex, as it affects the central nervous system, has been summarized by Mosberg and Arnold.[23] Three cases, each with a different yet frequently reported type of onset have been described by L. Boshes et al.[2] It must be emphasized that cryptococcosis is seen co-existing in conditions of malignant lymphomas, in endocarditis, pyelonephritis, diabetes and even in conjunction with other fungus infections.[24,25,26] The organism can often be demonstrated in spinal fluid directly by the India ink preparation,[27] or can be grown easily on Sabouraud's glucose at room temperature. The yeast-like cells are gram positive ovoid or spherical single-budding, thick-walled, 5-20 u in diameter, with wide, refractile, gelatinous capsules.

Symptomatology: Many cases of cryptococcosis have been incorrectly diagnosed as a form of chronic meningitis, notably tuberculosis, or even choriomeningitis. They may all reveal pleocytosis, elevated protein, decreased glucose and chloride content. Tuberculosis should not be accepted as a final diagnosis until the tubercle bacillus is demonstrated or at least until all other fungal diseases are excluded, particularly cryptococcosis. There are numerous cases of cryptococcosis on record where marked increase of intracranial pressure has raised the question of a space occupying lesion. Actually, this symptom picture is caused by a granuloma composed of organisms. The usual history is that of an individual in apparent good health until the time of a relatively mild cranial injury. Now there is developed the picture of increased intracranial hypertension. Spinal fluid may be clear, turbid, or even xanthochromic, containing up to several hundred cells per cubic millimeter. These cells are usually lymphocytes. Both sugar and choride levels are reduced while the protein is elevated. Wilson and Duryea[28] and Martin and Padberg[29] have reported cryptococcosis cases resembling the picture of subdural hematomata. Ley et al.[30] removed a torulogranuloma from the cervical cord of an eight-year-old girl in whom a spinal cord tumor was initially suspected. The diagnosis of cryptococcosis is not too difficult, providing it is entertained as a possibility in cases of acute or chronic meningoencephalitis of unknown etiology. Also, where there is long existing headache, the thought of fungus infection must always be kept foremost in the mind of the clinician at all times.

Treatment: Many types of management have been used in cryptococcosis but until recently none have been to any avail. Many patients die during the fulminating state of this disease or may live for many years in chronic invalidism with periods of relative quiescence. There have been remission periods of up to 20 years reported. Actidione, a new antibiotic cyclohexamide, has been used by numerous physicians in the treatment of cryptococcosis with serious complications resulting. Wilson and Duryea[28] discontinued this medication when some of their patients developed lethargy, ataxia and slurred speech, even though a sterile spinal fluid and a clinical arrest in apparently progressive cases had been achieved. L. Boshes and his group[2] felt that cyclohexamide precipitated the death of one patient in their series. Nystatin has been found ineffective. Several cases of improvement with 2-hydroxy-stilbamadine have been reported.[3]

Mycostatin has shown some promise. Cortisone and ACTH have been used with little or no effect. Recently several reports have appeared in the literature of apparent success with Amphotericin B. Biddle and Koenig[31] reported two such cases with apparent bacteriologic and clinical arrest.

ASPERGILLOSIS

This is a disease process caused by certain species of aspergillae and is characterized by the presence of inflammatory granulomatous lesions in meninges, orbits, eyes, external ears, nasal sinuses, the skin, lungs and sometimes in the bones. Aspergilli have always been common and troublesome fungus contaminants in the laboratory and hence the diagnosis is difficult to prove when suspicion is entertained for this organism. The organism is an aspergillus fumigatus which appears as broken fragments of hyphae with numerous small (2 to 3 u) round, green spores.

There have been few cases of aspergillosis recorded. Since the first report by Moniz and Leff[31] of a frontal lobe abscess due to aspergillus, there have been only nine reported cases involving the central nervous system, these in the form of an abscess or a granulomatous meningitis. There were perhaps some seven other cases involving the nervous system spreading from adjacent bone or as a result of systemic infection. However, none of these cases is authenticated. In most recent reports, two cases are recorded: one, in a 26-year-old soldier, which behaved like a posterior fossa tumor but pathologically proved to be a severe basilar and spinal granulomatous meningitis with an abundant growth of aspergillus fumigatus from the subarachnoid exudate. The other was a 10-month-old infant with a picture of basilar meningitis which pathologically revealed many granulomas in the cortex (Iyer et al.).[33]

Treatment: There is no specific management for this illness. The treatment of choice seems still to be iodide therapy. Nystatin, an antifungal antibiotic produced by streptomyces noursei discovered by Brown and Hazen in 1951 and marketed under the trade name of Mycostatin has shown some promise in isolated cases. Localized abscesses should be drained and granulomatous areas excised wherever possible.

CANDIDIASIS

Candidiasis, moniliasis, or thrush, is a disease caused by the species of Candida, usually C. albicans, and is an acute or subacute infection in which the fungus may produce lesions in the mouth, vagina, skin, nails, bronchi, lungs, and occasionally a septicemia, an endocarditis or a meningitis. Distribution of this organism is world-wide and both sexes and all ages are affected.

The yeast-like fungus Candida albicans was discovered in oral thrush by Langenbeck in 1831 and first described by Robin under the name of Oidium albicans in 1853. Over 170 synonyms exist today. The organism is believed to reach the meninges by way of the pharynx or even through the blood stream. It also has been noted that secondary monilial infection is possible after prolonged use of antibiotics such as aureomycin and terramycin. The clinical picture is that of a low-grade meningitis. There is a pleocytosis, not too high, but the protein content is elevated while the glucose and chloride content is diminished. The diagnosis is confirmed by the identification of the organism Candida albicans, a small, round or oval yeast-like cell 2-6 u in diameter. It is a budding, thin-walled structure attached to hyphae at various points of constriction.

Treatment: There is no specific treatment but general management consists of the usual supportive measures. Sodium iodide and Mysteclin, a new antifungal antibiotic containing mycostatin, are usually combined with the administration of ordinary broad-spectrum antibiotics. Mycostatin also has shown remarkable effects in some of these systemic monilial infections. Steroids and irradiation have been used. S. L. Zimmerman et al.[34] reported a case of monilia meningitis, hitherto fatal, treated successfully with streptomycin. Finally, Amphotericin B has been very effective in an occasional case.

SPOROTRICHOSIS

This is a chronic infection which ordinarily begins as a subcutaneous nodule, usually at some site of injury on the hand or forearm, progressing to lymphatic channels and lymph nodes draining the area. Lesions occasionally occur on other exposed surfaces but very rarely is the infection systemic. This illness is world-wide and both sexes and all ages are susceptible. The organism causing the disease is Sporotrichum schencki.

Rarely is the nervous system affected but a case of sporotrichosis meningitis has been reported by Hyslop et al.[35] Seen was a gelatinous form of meningitis at the base of the brain and present was a 2-cell count with 160 spores in each cubic millimeter of spinal fluid. The organism is a delicate, branching septate hyphae with spherical or oval conidae 2-6 u in size.

Treatment: The treatment of choice is still potassium iodide by mouth, with dosages up to 40 drops twice a day. Occasionally, sodium iodide intravenously, in intractable cases, has been used with some success. Stilbamadine, thymol, x-ray and surgery may also prove useful. Other drugs, including Nystatin, Amphotericin B and Nepara have shown some success but have not been used sufficiently to warrant more reliable conclusions.

MUCORMYCOSIS

This is a rapidly progressive and usually fatal disease characterized by acute infection or vascular thrombosis caused by invasion of the walls and lumina of blood vessels by the fungi. Diabetes mellitus appears to be a precipitating factor to infection, and pulmonary mucormycosis in the diabetic is usually rapidly fatal. It is also seen in leukemia and multiple myeloma, particularly after treatment with x-ray or with steroids. Mucormycosis of the central nervous system presents this triad: 1) uncontrollable diabetes, 2) orbital infection, 3) meningo-encephalitis. Direct infection of the brain and meninges by the paranasal sinus and orbit is well established. The organism is called "mucor" because of width—6 to 50 u—and is non-septate.

Treatment: No known treatment is yet available for this infection. Some new antifungal agents are at present being investigated to include 1) Candicidin, which is a strong fungicidal agent but, unfortunately, is too toxic;[36] 2) Nepera, which is made from streptomyces aninophilus and seems to show promise;[37] and 3) Eulicin, which is made from streptomyces paruns and is also considered fungicidal.[38]

CHROMOBLASTOMYCOSIS

This is a misleading name because the fungi in this group do not form blastospores or buds in tissue but have a characteristic brown color. Known also as verrucous dermatitis, it is caused by a variety of fungi which show watery formations of cutaneous nodules ultimately forming prominent papillomatous vegetations which may ulcerate. Generally the lesions are confined to the lower extremities.

This disease has been reported in various locations in Asia. Binford et al.,[39] as well as King and Colette,[40] respectively reported cases of mycotic brain abscess due to Cladosporium trichoides. There was recovery in the first case, possibly due to the use of penicillin and sulfadiazine which, however, proved ineffectual in the second instance.

HISTOPLASMOSIS

This illness is endemic to the central and the east central portion of the United States but cases have been reported from various other areas not only on this, but on other continents. It is caused by Histoplasma capsulatum, which is a diphasic organism growing as a mycelial saprophyte in soil and as a yeast-like organism in infected tissue. Histoplasmosis as yet has not been proven to be spread from man to man.[41] While it does not affect chickens, it has an unusual relationship to chicken excreta. Although most classifications of this type of illness seem relegated to the pulmonary area, there are disseminated lesions elsewhere in the body. There are, however, few reports of histoplasmosis of the central nervous system.

Treatment: The treatment of choice is, at the present time, Amphotericin B. Stil-

bamadine has been effective in only a few cases. Actidione, Amebacide,[42] and Cycloserine[43] have proven ineffective, as has Nystatin, which is not only ineffective but also toxic. However, the sulfonamides appear to have fungostatic properties at dosages sufficient to give blood levels of 10-15 milligrams per cent.[44] A combination of Amphotericin B and sulfonamides shows promise.[45] Triple sulfonamides have been used successfully in disseminated and mucocutaneous histoplasmosis.

Conclusion

It is my belief that we are entering a new era for the management of fungus infections of the central nervous system which heretofore have proven resistant to any and all treatments. At this time I may state that Amphotericin B has the most apparent effectiveness in most of these diseases. It is foreseeable that there will be other drugs of this nature which will serve to make the formidable panorama of fungus diseases less threatening in the future. With the upsurge of interest in the area of medical mycology, we can expect newer and more potent agents to appear, not only as therapy for the alleviation of the dread symptom picture, but also as a means for ultimate and complete recovery.

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A Method for Measuring Thermoregulatory Reactivity in Psychiatric Patients

JACK C. WESTMAN, M.D.

Alterations of homeostatic mechanisms in psychiatric illness have been reported by many workers. These disturbances reflected by impaired maintenance of homeostasis have been interpreted as signs of physiological dysfunction in mental disease. For the most part, studies have employed two principles, as outlined by Hill:[1] 1) the measurement of physiological processes that are ordinarily held relatively constant by homeostatic mechanisms; for example, blood constituents that show a "normal range," and 2) the measurement of the homeostatic response to an induced alteration in the physiological process; for example, studies evaluating the response of an organism to "stress." In the second instance one is concerned with a) the adequacy of the homeostatic mechanism in restoring a steady state to the function altered and b) whether or not the restoration to a steady state is prompt or delayed.

Various aspects of the autonomic nervous system have been subjected to experimental scrutiny in mentally ill subjects. Alterations of blood pressure, pulse rate, metabolic indices, chemical and physical constituents of the blood, circulating hormones and enzymes are mentioned in the literature.[2-7]

The study of body temperature regulation provides another method for evaluating autonomic responsiveness. The fact that hypothalamic centers play major roles in heat production and elimination is well documented.[8-10] A group of studies have focused on the measurement of the homeostatic response to an induced alteration in body temperature. Finkelman and Stephens[11] immersed schizophrenic and control subjects in cold water baths. They found that heat production, as measured by oxygen consumption, increased to a lesser extent and that body temperature fell to lower levels in the schizophrenics. Similar findings were reported by Freeman,[12] who placed schizophrenic and control subjects in cold environmental temperatures. He, too, observed a greater decrease in the skin temperatures of the schizophrenics.

Freeman[13] also administered pyrexia-inducing dinitrophenol to both psychotics and controls, noting that the schizophrenics showed less increase in skin temperature and oxygen consumption than the controls. Further suggesting that schizophrenics have less effective homeostatic thermoregulatory mechanisms, Gottlieb and Lindner[14] observed that the body temperatures of schizophrenics varied in closer harmony with changing environmental temperatures than with controls. On the other hand, Buck and his group[15] reported opposite results. They placed schizophrenic and control subjects in cold water baths and noted that the body temperatures of the schizophrenics were rigid with little fall in contrast with controls who showed a steady fall. A similar experiment with healthy men by Behnke and Yuglou[16] demonstrated temperature falls corresponding to those noted in Buck's controls.

Lindner and Carmichael[17,18] suggested the presence of a physiological thermal abnormality in schizophrenia. Their work did not involve the application of "stress." They noted that the mean difference between oral and rectal temperatures was less in schizophrenics than in controls. All these investigators concluded that differences did exist when psychotic and control subjects were compared.

The purpose of this paper is to describe a simplified method providing a stimulus to a subject's thermoregulatory mechanism whereby the homeostatic response to the stimulus may be measured. The procedure

From The Neuropsychiatric Institute, Ann Arbor, Michigan.

employs the ingestion of water of standard temperature and quantity by a subject in a basal, resting state with concurrent, continuous measurement of his rectal temperature.

Method

Each subject was placed at rest on a hospital bed two hours following the last meal. An electronic device for registering change in temperature was then introduced rectally.[19] Copper and constantan thermoelements enclosed in thin polyethelene tubing were inserted 5 to 8 centimeters into the rectum. The reference elements, one for each thermocouple, were imbedded in ice. The voltage resulting from the temperature difference between thermoelements was measured at two-minute intervals through a potentiometer and galvanometer. Voltage changes paralleled variations in temperature, permitting the direct conversion of voltage to temperature units. Readings were noted for at least thirty minutes prior to the rapid ingestion of 300 cc. of ice water at 7° C. Recording was continued for approximately sixty minutes thereafter.

Results

This procedure was employed with 108 subjects, 10 healthy university students and 98 in-patients from the Duke Hospital Psychiatric Service and Butner State Hospital.

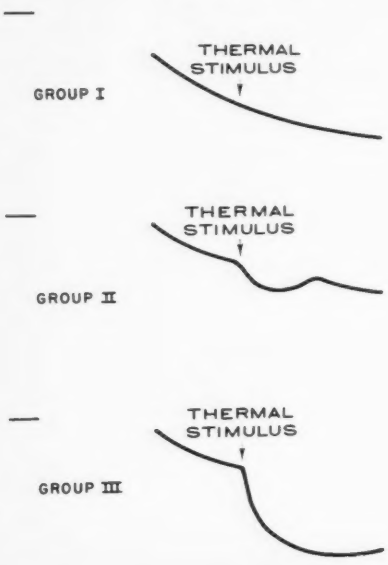

Figure 1.

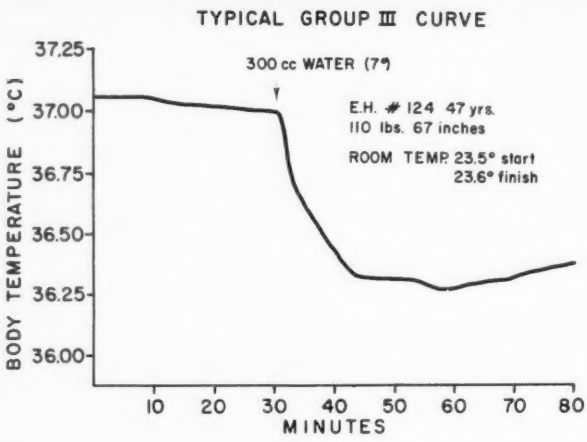

Figure 2.

The recorded diagnoses of the patients were as follows: schizophrenic reaction, 32; manic-depressive reaction, 24; psychoneurosis, 19; organic brain syndrome, 23.

The temperature curves obtained were separated into three groups as indicated in Figure 1. Group I curves were characterized by the absence of a discernible alteration in body temperature following the ingestion of the ice water. Group II curves displayed an initial deviation in body temperature with prompt restitution to the original curve pattern. Group III curves displayed an initial deviation in body temperature with prompt restitution to the original curve pattern. Group III curves were distinguished by a gross alteration in rectal temperature without significant restitution. A typical group III curve is reproduced in Figure 2.

All of the controls and 55 of the psychiatric patients exhibited Group I and Group II curves. Group III curves were only obtained with the 43 remaining patients (Table I).

TABLE I

Distribution of Temperature Curves Among Subjects

	Controls	*Patients*
Group I	5	11
Group II	5	44
Group III	0	43

When the curves of the psychiatric patients were classified according to diagnostic category, no significant relationship was observed between clinical diagnosis and curve pattern.

Twenty-two patients had been hospitalized for two years or longer. Of these, 12 exhibited Group I and II curves and 10 Group III curves, suggesting that duration of hospitalization was not a factor predisposing a subject toward a Group III pattern. The type of curve was not associated with residence at Duke Hospital or Butner State Hospital. Age, sex and total body surface were not related to the curve pattern.

In order to evaluate the possibility that the ingested water might affect the rectal temperature by contiguity within the abdominal cavity, axillary and rectal readings were made simultaneously on five subjects. The two curve patterns obtained were identical in each case.

Discussion

The purpose of this report is to call attention to a means of assessing thermoregulatory responsiveness in mentally ill subjects. The procedure employed in this study contains several uncontrolled variables, significantly limiting the conclusions that can be drawn from the results: 1) the stimulus was not given with the subject in a strictly basal state; 2) the room temperature varied within .2° C. during the period of recordings; 3) the routine, daily activity and living circumstances of the subjects were not uniform; and 4) the number of controls was not sufficiently large to permit reliable statistical analysis. It would, therefore, be desirable to modify this method by conducting the procedure at a uniform early morning hour following at least a 10-hour period of fasting in a room providing constant environmental temperatures.

With the limitations of our method in mind, the differences in temperature curve patterns noted appear to be sufficiently well defined to suggest that they may point up significant trends. Two related physiological studies seem to corroborate our findings in the control subjects. Without using a thermal "stress," Cranston[20] obtained smooth, declining cooling curves on healthy, quiescent males similar to those of Group I in this series. Stengel and Hopkins[21] found that the intragastric temperature in a group of non-psychiatric patients returned to previous levels in 30 to 45 minutes under conditions similar to those of this study.

The inference may be drawn that Group I and Group II patterns indicate thermoregulatory mechanisms capable of rapidly and effectively restoring homeostasis following a cold stimulus. A group III curve may point to "sluggish" thermoregulatory responsiveness. Mentally ill subjects, regardless of diagnostic classification, did show Group I and II curves in this series, but none of the control curves were of the Group III pattern.

Summary

1. A method has been described for measuring one facet of autonomic function: the production of body heat through thermoregulatory mechanisms in response to a cold stimulus.

2. Ninety-eight hospitalized psychiatric patients and ten healthy controls were studied employing this method.

3. The temperature curves obtained could be classified according to three distinct patterns of response to the stimulus.

4. The psychiatric patients displayed response patterns I, II and III, however, the controls did not show Group III curves.

Author's Note: Grateful acknowledgment is made to Dr. Hans Lowenbach, Duke Hospital, Durham, N.C., for his suggestions and to Dr. James W. Murdoch of the State Hospital at Butner, North Carolina, for his cooperation in obtaining subjects.

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Librium as an Adjunct to Psychotherapy in Private Psychiatric Practice

NINA TOLL, M.D.

While psychotherapy is recommended for the resolution of deep-seated emotional conflicts, the presence of such symptoms as anxiety and tension often renders the patient inaccessible to a meaningful therapeutic relationship. Fortunately, since the advent of chemotherapeutic drugs in psychiatric practice, the therapist's problem in obtaining full patient cooperation has to a large extent been overcome. While the conflicts themselves may not be resolved by the use of these drugs, reduction of anxiety or increase in ego strength will in many cases facilitate psychotherapy. However, certain drugs may affect psychotherapy adversely. Newbold et al.,[1] for example, have suggested that while chlorpromazine may reduce internal disturbance enough to allow good therapist contact, psychotherapy is sometimes impeded by dulling the effects and/or the motivation for treatment. Furthermore, discontinuance of chlorpromazine increased affect, making psychotherapy impossible in several instances.

The present report is concerned with an evaluation of a new psychotherapeutic drug, Librium, as an adjunct to psychotherapy. At a recent symposium, several investigators reported that during and following treatment with Librium patients were definitely more accessible to psychotherapy. Tobin et al.,[2] observed an increased productivity of speech and ease of association during therapeutic interviews, with patients volunteering the remark that they felt freer in expressing themselves. Similarly, Constant[3] found that in both depression and tension states, patients were better able to verbalize their difficulties and hostilities. Several obsessive compulsives treated by Bowes[4] also became more amenable to psychotherapy. Sussex[5] speculated that Librium may prove a valuable adjunct to psychotherapy in mixed neurotic states. Most of his patients who had had no symptomatic improvement from any other mode of treatment remained symptom free following initiation of therapy with Librium.

Materials and Methods

Sixty-five patients (22 men and 43 women) between 20 and 60 years of age, the majority of whom were between 30 and 40, received the drug. Diagnostically, they were distributed as follows:

Neurotic reactions	50
Pseudoneurotic schizophrenia	4
Catatonic schizophrenia	3
Paranoid condition	3
Manic depressive depressed	4
Rheumatoid arthritis	1

The presenting symptoms were tension in 38, anxiety in 30, depression in 18, insomnia in 14, alcoholism in seven, withdrawal in eight, irritability and overweight each in

Librium is the trademark for Methaminodiazepoxide, Hoffmann-La Roche Inc., Nutley, N. J.

four, epigastric pain in four, claustrophobia in three, obsessive compulsive, impotence, ideas of reference each in two and one instance each of tension headache, anorexia, depersonalization, gastric ulcer, frigidity, paranoid delusions and backache.

The drug was given regardless of diagnosis to all patients in need of a tranquilizing drug and/or whose response to previous agents, such as Compazine, meprobamate, etc., was not satisfactory. It was deemed not necessary to employ placebos or control medications, since the condition of the patient prior to the institution of therapy with Librium was well known, and the inadequate response to other drugs served as a basis of comparison.

Practically all of the patients were treated in individual and/or group therapy prior and throughout the period of administration of the drug, and therefore seen regularly, at least once or twice a week.

Dosage

Librium was administered orally in doses from 30 to 55 mg. daily, either 10 mg. t.i.d. or 25 mg. b.i.d. In cases of insomnia 25 mg. was usually sufficient at bedtime, except in one patient who took up to 45 mg. only at night. There seemed to be no difference in effect between a dosage schedule of 10 mg. t.i.d. plus 10 mg. at bedtime, and 25 mg. b.i.d. This fact may possibly simplify the administration procedure in certain cases. Ten milligrams were given in two cases where sleepiness was a side effect.

Increasing the daily dose beyond 50 mg. did not improve therapeutic results. As improvement continued, the patients themselves spontaneously reduced the dosage by "forgetting" to take the drug.

In seven patients with depression Librium was used in combination with Tofranil. Three of them lost the symptoms of depression but became manic within a few days, and one of them had to be hospitalized because of this. It is impossible to determine whether this effect was due to Librium, to the converging effect of Librium and Tofranil, or to the well-known occasional side effect of Tofranil.

Results

The overall results may be summarized as follows:

Marked improvement	30
Moderate improvement	18
Minimal improvement	10
Unchanged or worse	4
Recovered from depression, but in a few days became manic	3

The best results were obtained in the patients with neurotic reactions, 75% of them showing marked or moderate improvement. Of the 13 neurotics who either did not improve, or showed minimal response, six were alcoholics and six had added physical conditions or severe situational factors complicating the disorder. Three out of four manic depressives were unimproved, and one of three with catatonic schizophrenia did not respond at all.

In most cases improvement was evident within a few days. If no improvement was achieved within a week there seemed to be no advantage to continue the patient on the drug beyond that time. No withdrawal symptoms were noted even though in some cases the drug was suddenly discontinued.

There was a definite facilitating effect on psychotherapy, which may have been due to diminished anxiety and release of excessive control.

Side Effects

Few and relatively mild side effects noted were tremulousness, sleepiness, constipation, dryness of mouth, "light-headedness," overstimulation, "heavy head," and change in taste (water tasted flat, and sugar much sweeter). Of 65 patients, 53, including one pregnant woman, had no side effects whatsoever. The drug was not only well tolerated but the patients took it willingly, preferring it to all other tranquilizing drugs they had taken previously. Librium seems to potentiate the effect of alcohol, and therefore it is important to warn the patients to abstain from drinking while taking Librium.

Among the favorable side effects were mild euphoria, vivid dreams, which frequently helped progress in psychotherapy,

and in one patient, an unexpected amelioration of a neurodermatitis of many years' duration which was resistant to all previous treatment.

Comment

As is true of other tranquilizers the question of whether improvement reflects a change in the underlying pathological process or only relief of the discomforting symptoms may be debated. Our experience of approximately six months with the drug would lead to the conclusion that Librium definitely provides prompt and dramatic symptomatic relief.

Concerning the particular patient whom the drug benefits, it is of interest to note that the neurotics responded markedly and in the greatest numbers. Improvement occurred in both men and women, there being apparently no sex-connected difference. The extreme euphoria verging on manic symptoms in the depressive cases would suggest that Librium may be contraindicated in severe non-neurotic depressions. However, further study of its use in such patients is warranted.

There seemed to be no correlation between the type of symptom and the dosage or the length of treatment. The effect of Librium was exceedingly prompt—even 10 mg. often relieving anxiety or tension within 15 to 20 minutes. The ready acceptance of the medication by all the patients may in part be accounted for by the prompt relief of anxiety, the lack of serious side effects and to the definite although mild euphoria.

The effect of Librium on the symptom of excessive withdrawal and tension (excessive control) is remarkable, and may be illustrated by the description volunteered by one patient, a teacher: "I think it is miraculous. I was feeling outgoing. The effect was so liberating that I felt excited and very outgoing, without the nervousness that comes with Dexamyl. I would walk into the class completely unprepared and end up well. It made me become less involved with myself and my state of mind was outgoing."

Summary

Librium was administered to 65 patients in private psychiatric practice adjunctively to individual and group psychotherapy.

The therapeutic effect was most marked when the predominant symptoms were tension, anxiety, withdrawal, insomnia, and general irritability. Symptoms of depression, anorexia and depersonalization were moderately affected, and alcoholism, overweight, impotence and frigidity were unaffected or only minimally changed.

The drug acts promptly in relieving anxiety and tension, but equally dramatic was the improvement in three cases of paranoid condition, where previous therapy with tranquilizers had only a moderate effect.

Except for patients with manic depressive psychosis in whom Librium may be contraindicated, the side effects are few and extremely mild.

On the basis of this study Librium is indicated for patients with neurotic reactions and should prove to be a most useful drug both for symptomatic relief and for facilitating psychotherapy.

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The Anxiety Reaction in Reference to Existential-Analytics

G. M. DAVIDSON, M.D.

> Striving for Life, I seek death; seeking death I find life.
> *Shakespeare.*
>
> Die and Become.
> *Goethe.*

According to the Diagnostic Manual[10] of the American Psychiatric Association, anxiety reaction is a sub-type of the psychoneurotic disorders, one of the larger group of disorders of psychogenic origin. Anxiety reaction is further differentiated in the Manual as a reaction which is diffuse and not restricted to definite situations or objects, as compared with the phobic reaction. Anxiety reaction is analogous to the former term "anxiety state." To quote the Manual again, phobic reaction constitutes a detachment of anxiety from a specific idea, object, etc., displaced to some symbolic idea or situation; it is cited as synonymous with the earlier term "phobia" and includes cases formerly classified as "anxiety hysteria." The term "anxiety state" coined by Hecker, was quoted by Freud in 1893 to differentiate a clinical syndrome from neurathenia, then in vogue. Freud[15] in 1894 and 1908, paying tribute to the times and seeking specific causes responsible for clinical manifestations, introduced "anxiety neurosis." This term he used to denote a condition resulting from faulty sex practices, differentiating it from a condition of conflict between desire and fear of sex. The latter he called "anxiety hysteria." Psychiatric thought was not satisfied with these concepts and switched back to the "anxiety state" of Hecker, which later was changed to the present term "anxiety reaction."

It is often very difficult to define a psychiatric condition, a matter which I have discussed elsewhere.[8] However, it is evident that far reaching results can be obtained by looking at old things in a new light. Toward this end I like to quote this existential philosophy of Karl Jaspers:[18]

> "We always live and think within a horizon. But the very fact that it is a horizon indicates something further which again surrounds the given horizon. . . One runs into the infinite unless one arbitrarily sets a limit by some unquestioned purpose or contingent interest. And in that case, precisely at these limits, one always runs into bewildered difficulties."

Perhaps we can say in speaking of anxiety reaction, that we are facing a horizon which is surrounded by a wider one of psychoneurosis. Looking further one can envisage the horizon of disorders due to psychogenic causes surrounded by the wider horizon of life itself. I propose to examine the anxiety reaction with the aid of a "new look" of existential analytics with the hope that the additional direction will contribute to better understanding of its nature and better methods for its treatment. Clinically I shall call the first horizon the immediate horizon of clinical semiotics of anxiety. The second horizon is a cultural-ontological one. We shall speak of the third and fourth horizons as the anthropological-existential. There is no sharp demarcation among the horizons; in fact, they are interwoven. It is only for academic purposes that they can be discussed separately. It follows that one may see the immediate horizon as a *Gestalt* (syndrome) which has for its background the other horizons which will permeate the *Gestalt*. Due to various causes the permeation will be of different degrees. As a result the *Gestalt* may become rigid, unstable, etc.

For clinical reasons it is necessary to establish a set of activities for the human being that could be maintained under set circumstances. Such a set of activities is known as a clinical syndrome.[6] Regarding the clinical syndrome of anxiety the following symptoms are observed:

1) Generalized painful tension which tends to accumulate to a degree that the patient is unable to tolerate;

2) Irritability of a generalized type due to accumulated tension;

3) Sensation of choking which causes fears and panic states (the word anxiety stems from the Latin, to choke or throttle);

4) Anxious expectations expressed in various ex-

pectations of calamities about to befall the patient or people close to him, described by Freud as "pangs of conscience";

5) Doubt and indecision;

6) Insomnia; and

7) Physiological reactions at various levels of personality, such as disturbances of the respiratory, G.I., cardiovascular, etc., systems which may accompany anxiety.

A clinical picture of an acute anxiety attack is as follows: The face is practically immobile, pale and cold; gestures are slow, vocalization is interrupted by long pauses; facial expression is one of helplessness. Pupils are dilated, pulse fast, and blood pressure increased. The patient feels oppressed, almost annihilated. He has difficulty in concentration and thinking. There is choking, giddiness, nausea and vomiting. Vision may be blurred and acroparaesthesias may be present. There is resemblance to a state of panic, or a state preceeding fainting; the latter may occur as a sequel of vertigo.

The acute attack may last from one to several hours, vary in intensity and end suddenly. On the other hand attacks may become chronic. During anxiety-free periods the patient may regain his psychical equilibrium.

As in any emergency a sympathetic-adrenal response will set in with changes in the internal milieu. The organism is prepared for fight or flight. As in any other defense, anxiety, using defense forces may outwit the cause of the attack. The polarization of defense forces of the total personality over a long period of time will result in a vicious cycle difficult to undo, and may progress to chronicity of reaction.

Euziere and Margaret[12] in their interpretation of the physiological manifestations of anxiety consider the facial pallor due to vasoconstriction of vessels of the hand caused by action of the cervical sympathetic. The bitter taste in the mouth, the feeling of a parched throat is explained as a consequence of inhibition of the vasodilators of the tongue and salivary glands. The palpitation of the heart, etc., is caused by predominance of cardiac sympathetic over the vagus. Shivering, goose-skin, tremors and trembling, human cybernetics (homeostasis) result from a continuous and delayed feedback of information from muscle, tendon and joint essential for muscular coordination. The delay may be due to local damage in a small group of cells which suggests a time-lag in the normal mechanism of muscular action. The ascending neural impulse may have to travel a round about way, so that the muscle overshoots the mark. Thus tremors are caused by a time-lag in the facilitary system which maintains muscle-tone; shivering by a long circuit through the posterior hypothalamus (as the physiological reaction to cold); trembling by similar long circuiting due to the disturbing effect of anxiety and fear.

According to Pavlov, anxiety is due to the inability of the organism to develop a new dynamic stereotype in reaction to new demands upon the organism by internal and external stimuli. The difficulty appears in a disturbance of the first and second signaling systems and is due to weakness of central inhibition.

The question arises whether anxiety may be centrally engendered. Burridge[4] observed that neurons are rhythmic tissues in constant state of activity and excitation is an act of addition, not an act of striking, as commonly thought. Lashley[21] postulated that the brain works in *toto* aided by facilitating areas. Lorente de Nó[23] found self-exciting chains of internucial neurons in the brain. Magoun[24] has shown that stimulation of the ascending reticular formation of the brain stem results in desynchronization of electro-potentials evidenced by something like a state of tension and anxiety. The reticular formation connects with hypothalamic, thalamic, and midbrain areas which are also engaged with the mechanism of central elaboration of emotion as shown by Papez.[25] Since there is no thought or memory without an affective component the latter may be considered an igniting central (as well as peripheral) agent in anxiety.

The evaluation of cultural and ontologic aspects of the problem of anxiety reaction raises the question of definition. What do we understand under culture and ontology? I like the view of J. C. Shairp (quoted by

Webster[30] that the word culture has something artificial about it and that the Greek *paideia* and the Roman *humanitas* is preferable. However, for clinical purposes the definition of culture given by Webster is acceptable. The word comprehends the complex of distinctive attainments, beliefs, traditions, etc., which constitute the background of a racial, religious, or social group. Ontology may be treated philosophically with an aspect of metaphysics but for the clinician ontology has to be treated as the developmental history of the individual. How far back in the history do we go? To separate phylogeny from ontology the medical dictionary speaks of ontology as a process stretching from the fertilized egg to adulthood.

We cannot separate culture from ontology, since the individual is not brought up in a vacuum but in space-time continuum. However, contributions on the subject are colored by the philosophy of the individual author who emphasizes one or other aspect of the process. Freud gives a most elaborate clinical ontological structure of the psychological growth of the individual. He offers theories on axiety, not its final solution, nevertheless psychoanalysis sees the origin of anxiety in birth trauma and fear of castration. Together with Rank[27] he sees in birth trauma a threat of "separation" from mother later elaborated by fear of loss of mother, fear of loss of phallus, fear of loss of social approval, and fear of loss of life (death). This is an example of the pursuit of a process from the standpoint of "linear progress." However, it is essential to pursue a process not only as to its linear progress but on lines of "multidirectional influence."

Of other ontological attitudes, attention is called to Adler's[1] contribution on "biological inferiorities" with which the individual is born, and his compensatory attempts which may also progress to an elaborate system. Jung[19] did not occupy himself much with anxiety but his concept of the collective racial unconscious pushes the inquiry further. In contrast the approach of Horney that anxiety originates in the conflict between dependence and hostility, takes on a more immediate cultural-ontological view. Regarding the pursuit of ontogeny from fertilized egg onward, the observation of Corner[5] is of interest. This author comments that human life commences with the Pilgrim's Progress starting with placentation (adaptation) the beginning of an unending process of getting along with the world.

Linton[22] called attention to the psychic needs of the individual: security, recognition, emotional response, and new experiences. I like to add the need of communication, perhaps the most distinct for man. I prefer to call the needs affective in lieu of psychic for the reason that a need implies affect. Moreover, I regard affectivity as the final common path of the total personality.[7]

The affective need of security originates in the helplessness of infancy and its prolongation into adolescence and further (compare with the conflict of dependency and hostility—Horney[17]). The insecurity is activated by any encounter with challenges of life (work, love and social obligation.—Adler[1]). The psychoanalytic emphasis on fear of loss of mother, fear of life and fear of death, etc., is in evidence, testifying to the multiplicity of factors rather than to specific causes of release of anxiety. The following is an illustrative situation:

> A college student, age 21, had developed considerable anxiety in reaction to failure in her work. She tried to combat the anxiety by overeating. She gained considerable weight which aggravated the situation. She evidenced an Oedipal complex having great dependence on and hostility toward her mother with attempts at separation with subsequent panic states. She recalled as an early memory, perhaps at the age of five, that her mother impressed her with the need of self-dependence. She remembered that whenever mother would admonish her, she would hold on to her dress symbolizing self-dependence by holding on to herself in that way. It was this failure of self-dependence that was the driving force behind her anxiety. The most striking effect was feeling of anguish in anticipation of annihilation. Patient was successfully treated psychotherapeutically. She graduated, married, and remained well adjusted during a follow-up of five years.

The need of recognition may be found in any culture. The need applies not only to libidinous values but to other considerations

as well: honor, prestige, power, etc. The stories about the American Indian by James Fenimore Cooper, or the stories of the glorified heroes of the West offer ample testimony to this. The following case may serve as an example.

A young man, 28 years of age, the only son, the center of attention at home, at school, at work, and with the opposite sex had been suppressing his drives for the sake of becoming an executive officer in his company. He succeeded at the cost of severe anxiety reaction marked by practically all the classic symptoms. Active psychoanalytic psychotherapy was successful in rehabilitating him. He married and raised a family.

The affective need of new experiences seems insufficiently appreciated. In this respect I like to quote A. N. Whitehead:[33]

". . . one main factor in the upward trend of animal life has been the power of wandering. Perhaps this is why armored plated monsters fared badly. They could not wander. Animals wander into new conditions. They have to adapt themselves or die. Mankind has wandered from the trees to the plains, from the plains to the sea coast, from climate to climate, from continent to continent, and from habit of life to habit of life. When man ceases to wander he will cease to ascend in the scale of being. Physical wandering is still important, but greater still is the power of man's spiritual adventures, adventures of thought, adventure of passionate feeling, adventure of esthetic experiences. . . ."

The essence of the need is readily discernible. On the positive side the need is the background of research, invention, and new ideas. On the negative side the need may evolve into a "wanderlust," and so-called psychopathic behavior of which psychopathology offers evidence. The following case illustrates a situation:

A man, age 38, a musician, was seen because of his unbearable anxiety provoked by frustration of the pursuit of what he called "experimentation toward understanding life." His experiment consisted of traveling in search of new experiences, particularly sexual that he intended to write about. He was an illegitimate child adopted by his maternal grandmother. He remembers himself at the age of five being taken for an extended auto trip. He enjoyed the active experience so differenta from his life at home. A year later he was taken on a voyage. He felt "worldly." In contrast to these events he remembered while ill and confined to his room that he felt like a "prisoner." He engaged in sex play with girls and boys and was seduced by an older woman at the age of 12. During the war he enjoyed his service in the Navy. Since his discharge he was twice married and had numerous contacts with women. He masturbated to excess in order to combat anxiety. He did not stay in psychotherapy, quitting after a few sessions in order to return to his home town to investigate his origin.

The affective need of communication evolves from the need of companionship, which in turn originates in the dependency of infancy. That the need is distinct is seen by the fact that one cannot exist in isolation. The latter may lead only to mental death, deterioration or suicide. We know that even in advanced stages of schizophrenia, there is some interpersonal communication even though hallucinatory. The hermit is not alone which can be deduced from the observation of Thomas á Kempis in his *Imitation of Christ* of "being alone with God." Another most interesting observation is the concept of Martin Buber[3] on "I and Thou."

The individual may express vulnerability of more than one affective need as is exemplified by the following case:

A woman, age 42, married, socially and politically minded, had been in psychotherapy for a number of years because of intolerable unrelieved anxiety. In fact, her anxiety reactions became chronic, appearing as if a conditioned reflex response to the numerous frustrations of life. Mental exploration showed that the patient had developed exaggerated needs of security, of recognition, of new experiences and of communication. She was the first born and the only child for three years. Later a brother was born who she felt deprived her of her birth right. She developed considerable ambivalency toward her parents and the brother, and resented her feminine role aspiring to symbolic masculine superiority. She projected her hostility upon her husband with death wishes and frigidity, thus compounding her conflict by damming-up libido. She was looking for magic help from the therapist to change her personality and since this did not materialize was changing therapists.

This case illustrates the danger of identifying abstract thought with concrete facts (patient reacting to a superstructure alien to herself) resulting in the familiar situation of creating a problem by trying to solve it, of worrying because one worries, of being afraid of fear, etc. She finally became aware of her mental operations. For instance, of her insecurity which was a reaction to an

abstract idea that in emergency she would not be able to care for herself. She realized that this was not the case but that she was afraid of not being able to acquit herself adequately in an emergency.

I like to refer to the observation of Linton that the form which behavior assumes cannot be explained in terms of the motivation needs alone. The needs are shaped by a multitude of forces. The behavior which satisfies one or a number of needs is organized in respect to the environment, the person's life, and his total of experiences. Cultural influences fall in line with the "multidirectional" influences on growth.

Anthropology is defined as a science of man or a science of being. Existential philosophy is also interested in being. It has, however, a metaphysical aspect altered from a science of being to a study of the conditions of knowledge. In the history of man a most dramatic event in the course of the process of life is the appearance of sexual generation. With its appearance, the self-sufficiency and the immortality of the asexual cell was as if condemned and gone, and a new cycle of fecundation, birth and death set in. This cycle grew to vast complexity as demonstrated by such activities as adaptation, natural selection and sparks of sudden mutation. This gigantic revolution may be paralleled only with the next revolution in the course of the same process of life, the appearance of man.

I like to call the triad of fecundation, birth and death the "original drama of the life process." This triad is reenacted in the life of the individual and is felt as keenly today as in remote times, with the difference that each epoch leaves an imprint on the mode reactivity to the problem but without substantial change in its deeper meaning. The essence of drama is not unhappiness but rather the solemnity of the workings of events and what they do—the inevitableness of events and the futility of escape (Whitehead). To illustrate, when the Neanderthal man buried his dead and thought to unite them as indicated by his cave paintings, does not this act indicate a belief in a life beyond? Or when a patient of mine, a sophisticated young lady under stress of sexual and religious conflict, revealed this state of mind while undergoing ether anesthesia: "One . . . two . . . three . . . count they said . . . leaving me alone to count my way into oblivion . . . swimming white coats . . . there is the sky now, and I belong to it . . . maybe God should be there too . . . I know the clouds are not, and even God does not exist . . . I am free of Him too, because I know what He knows . . . there is ringing blackness." Does this account not have the same echo as the first? It is obvious that both ventilated a projected conflict of the drama of the life process, both making an attempt at solution of the conflict.

In man the challenges of life are created, modified, and conditioned as much by his biology as by his psychology and culture. Challenges expand with his progress and reactions to them extend and project themselves into the infinite. It appears that man was never satisfied with his biological status. The added quality of "Mind" made him curious for the truth. At the same time man was afraid of what he may learn (fear of the unknown. This made him insecure and therefore required compensation, causing him to elevate himself beyond his biology to the point of suffering shame for his biological needs. This tendency led to overcompensation which made man place himself in the center of creation, god-like in form and quality and separated him from the rest of nature (White[23]). It curtailed progress because it delayed the understanding that the forces nucleated in man grew out of the environment and are returned to it.

Man is not a closed system composed of certain organs. He is an open energy system constantly receiving energy from the outside and constantly giving energy to the outside. From such a dynamic viewpoint organs are assembled bits of experience educated to work for the benefit of the total organism. It follows, that we should not speak of an organism but of a total organism or of a total personality. The totality is projected to the summit in conformity with the biological principle of "striving" to function to reach the top, as expressed by von

Economo in the concept of telencephalization. It follows further that the projected summit will be collective and experienced as "Mind." One can understand then that each cross-section of the totality will also have "Mind," making every manifestation of the totality psychosomatic (to be understood as a functioning ensemble and not referable to a conventional etiological meaning) and not dividing subjects from object. It makes both physical and psychical aspects of the totality equipotential, eventually allowing the totality to be measured by either physical or psychical methods. It also brings about new tools of investigation such as thought.

The new tool, thought, is double edged. On the positive side (providing thought has an adequate affective component meaning to give sufficient drive without rigidity), the power of thought compels us to search for truth by working out a philosophy of life in harmony with the times (freeing ourselves from ideas that have outlived themselves). On the level of thought we are able, under certain circumstances, to steal a glimpse into the future. On the negative side, the power of thought enables us to construct symbols of things apart from the things themselves which is a source of conflict. Existential philosophy offers on the positive side a new orientation which warns of the negative aspects of thought.

The derivation of the word existential is from the latin *ex-sistore* meaning to become or to emerge. It developed as a reaction to Scepticism which was the result of disappointment with Romanticism in the search for the Absolute. Existentialism caused Rationalism to emerge into things for themselves, to phenomenology before intelligence could cathegerize them. Consequently, Existentialism sees human existence as spiritual, because consciousness is fundamentally "emotive." This concept is in harmony with certain psychiatric thought that man cannot be identified only as *homo sapiens,* or *homo faber,* or *homo economicus,* or as a social contractor, or a political, or a libidinous animal. He is all of those things and more.

In the back of this is affectivity. Man is essentially an affective being, since he is the one and only creature that has human feelings. One may agree with Heidegger[16] that human existence is being-in-the-world. In saying "I" human existence expresses itself as being-in-the-world. Another fundamental existential experience is dread. The latter is experienced in the face of nothingness or nonbeing (compare dread of nothingness with the psychoanalytic fear of "separation" or fear of "loss" of mother or dread of annihilation). It is interesting to note that Heidegger considered dread physiologically conditioned (perhaps as a tribute to Nietzsche who spoke of "feeling with our bodies"). The "I" lives in the knowledge and dread of its own extinction and is challenged by going through a crisis of dread to affirm its humanity and fulfill its own potentialities. When the latter is achieved one speaks of "authentic" existence. In contrast is the conventional "unauthentic" existence which is "anonymity." The person will suffer guilt for not fulfilling his obligations. Guilt is interpreted by Heidegger not in the Judaeo-Christian sense but as indebtedness (the German word Guilt (Schuld) has both meanings—guilt and debt).

One of the most striking faculties of "being" is transcendence—the ability to transcend the immediate situation, thus transcending the trinity of time—past, present, and future. An outstanding aspect of transcendence is freedom which carries inexhaustible possibilities with it. Transcendence may also be interpreted as anticipation, meaning to go out beyond the given. Toward this end one may think in evolutionary terms of development of mind. To paraphrase Sir Grafton Elliot Smith[29] "anticipation may be observed on the level of primitive vertebrates." The dogfish scents food and pursues it, culminating in capturing the food and eating it. Thus is initiated the ability to anticipate the result of a given course of action.

Regarding the existentialist view on anxiety, Kierkegaard[20] sees anxiety as the consequence of actualizing freedom. The more freedom we have the more anxiety will we acquire (recall "escape from freedom" as elaborated by Fromm). Anxiety is also

spoken of as a consequence of emergence of self-awareness. A characteristic trait of anxiety is "maintenance of relation with the dreaded" which finds clinical confirmation. It is interesting that Kierkegaard also spoke of the educational aspects of anxiety. Existential philosophy speaks of anxiety as of "existential anxiety" or "ontological anxiety." In my opinion ontology, in a clinical sense, is the weakest point of existentialism which can be considered ontological only from a metaphysical viewpoint.

Binswanger[2] describes his distinction between anxiety and phobic reactions. In the former the world threatens to vanish and delivers existence to nothingness; there is intolerable horror. In the phobic reaction there is an attempt at preservation of a restricted world.

Man has tried since antiquity to solve the basic drama of the triad of sex, birth and death by way of a self cure by creating an illusion of immortality. One may observe the fusion of the constituents of the "triad" —birth, sex and death into one not only clinically but also on the lower biological scale. For instance, with reference to the latter, the ephemerides die during the sexual act. Clinically, cases of conversion hysteria, epilepsy, sexual deviation, etc. suggest that on the deeper level of the psyche, sex and death frequently fuse. "Poetic wisdom" is aptly expressed by Ronsard: "L'amour et la mort n'est qu'ne meme chose." One can trace the same insight in the stages of development of literature—Classicism in the work of Sophocles and others, Romanticism as elaborated by Mario Praz in "Romantic Ecstasy"; and the Realism of our times in the works of Alberto Moravia who in the "Woman of Rome" combines copulation with murder (death) and impending childbirth; and Cesare Pavese who in the "Moon and the Bonfires" pictures violence and fusion of sex and death as consuming as fire. Dostoyevsky in "Possessed" refers to the observation in the Gospel that there will be no childbearing in the Resurrection.

Sex taboos reflect the fear of fusion of sex and death from remote times. The fear became embedded in the deeper layers of the psyche and may be seen clinically in various symbolisms. The latter reaches a height of expression in dreams and paraphilias. A cardinal trait of paraphilia is avoidance of reproduction which is strikingly demonstrated in necrophilia.

Regarding dreams, attention is called to nightmares of annihilation of the post-traumatic states. As Kardiner puts it, the ego becomes body-bound. But it is not only in post-traumatic states that the ego acts that way. The experience of the trauma actualizes it as do other factors which constitute polarization of the affective needs of the individual.

An account of a series of dreams was given by a 21 year old girl. Dreaming of a rabbit that was snapping at her in the corn field, jumping at her and frightening her, as it followed her like the rabbit in Alice in Wonderland. (She liked to identify herself with Alice.) She also identified herself with the rabbit. This girl rejected her female role. She was attracted by and afraid of her father's penis. She produced a number of associations pertaining to ancient symbolization of the hare or rabbit, such as the ancient Greek belief that a female hare may have young without the male; that a male rabbit can also produce young; the Egyptian identification of the hare as a "leper," the symbol of Easter Dawn, and "to be created" carrying the wish and seeing it through to reorganize oneself. She wanted to join her father who was dead and rise to life again with him, but the fear of annihilation was in the foreground.

Another example of violence in dreams pertaining to fear of annihilation was reported by a woman, age 43, subject to recurrent anxiety attacks. The conflict between her fated role as a woman and masculine aspiration was shown by a fear of annihilation by way of the sexual act—"of being nailed" which she tried to escape by emasculating the man.

A comparison of the anxiety reaction with the phobic reaction may be seen in the following situation:

A middle aged woman subject to claustrophobia for many years gave a history of extreme hostility toward her mother starting in early childhood when she observed her mother swaddling her new-born baby sister. She felt in danger. Her claustrophobia began while pregnant with her son and while traveling in a subway. She suddenly felt upset as if the child was "buried alive." Later she frequently felt as if she were "being buried alive." Once when leaving the movies with her husband she felt that things were unreal and felt "trapped-in the world." She felt condemned to eternal suffering. Her par-

ticular phobic object was the elevator. She felt extremely agitated in one and was unable to use the self-service type. She felt threatened with complete disaster-annihilation. After working with her for some time the patient dramatized the situation by going up in a self-service elevator with her son. She was surprised that she could use it without fear and since then has been able to enter the elevator alone.

This situation seems in harmony with the interpretation given by Fenichel[13] and Feldmann (quoted by the former) that "mother's womb" type of claustrophobia (which seems to be the case here) expressed in fear of being buried alive, may be interpreted thus. That the feared room represents mother's womb and the interior of our own body. In both the anxiety and the phobic reaction there is a background of fear of annihilation, rooted in the original drama of the life process.

Summary

In the light of this presentation the anxiety reaction is rooted in what I called "the original drama of the life process," culminating in a fear of annihilation. The reaction is activated in a "linear" way of progress and facilitated by "multidirectional" influences. Anxiety may be regarded as a stepping stone in achieving "wholeness." To paraphrase Goethe it is "dying in order to become." Recurrent attacks of anxiety are a continuous attempt at achieving wholeness.

Therapy is basically psychoanalytic modified according to merits of the case. Modern pharmacotherapeutics may be used to alleviate anxiety. Existential analysis broadens the psychiatrist's outlook. It warns us that most tormenting problems may arise from identification of abstract thought with concrete experience. The accent is thus on "think-how" rather than on orthodox "know-how" to administer the most efficient therapy.

Manhattan State Hospital, Wards Island, N. Y.

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High Dosage Methylphenidate for Depression

CARL D. KOUTSKY, M.D., FLOYD WESTENDORP, M.D.,
and PAUL BRANSFORD, M.D.

Since its introduction in 1954 methylphenidate (Ritalin) has been reported as a psychic stimulator, a mood elevator, a psychic energizer, an antidepressant, a facilitator of verbalization and abreaction, an anti-withdrawal agent for schizophrenia, a mood-lifting substitute for alcohol in the treatment of alcoholism, a treatment for narcolepsy, and as a counteractant to barbiturate effects.[1-8]

The reports in the literature have consistently revealed a striking absence of serious toxic effects, although transient side reactions have been noted. The oral dosages reported for the drug varied from 10 to 90 mg./day, except for one report of 120 mg./day.[1] The usual intravenous injection dosage range to date has been 10 mg. to 30 mg. Because of its apparent safety in such a wide dosage range and its effectiveness as an analeptic, we decided to use very high dosages of methylphenidate in order to determine its efficacy in the more severe grades of depression.

Pharmacology

Although its mode of action is unknown methylphenidate stimulates both cortical and subcortical centers, having little effect on the central nervous system below the brain stem. The intensity of stimulation lies somewhere between caffeine and the amphetamines but its sympathomimetic effect is less than either. It causes no specific EEG changes. However, non-specifically there is a slight lowering of voltage and an increase in alpha activity.

It has minimal cardiovascular stimulating effects; an antagonizing effect on the carotid occlusions reflex pressor responses; no effect on cerebral blood flow or oxygen consumption; and has a mild bronchodilating action.[5]

From University of Minnesota Hospitals, Minneapolis.

Method

Fourteen patients hospitalized for symptoms of depression (all possible candidates for electric shock therapy) were chosen as subjects for trial on high dosage methylphenidate. The age range was from 30 to 64 years with a mean of 41 years. Ten of the patients had had previous major psychiatric treatment.

During the time of observation methylphenidate was administered to the patients in the following manner. The drug was started by giving 10 mg. orally every two hours for six doses beginning at 8:00 a.m. At one or two day intervals the oral dose was increased in increments of 10 mg. until 50 or 60 mg. were used. At the same time, in order to reach as high a dosage as possible the patient received intravenous injections of 10 to 30 mg. twice a day on the second or third day after the oral drug was started.

Decisions to continue or increase the drug were based on the clinician's judgment. If the patient responded in a positive sense and the drug could be utilized in the total treatment plan, it was continued. If no definite advantages were apparent, the drug was discontinued. The patients received methylphenidate from 6 to 30 days, with a mean of 22 days during the period of observation. Four patients were continued for longer than 30 days.

In order to standardize technique, the physician giving the intravenous methylpheni-

TABLE I

Effects on Symptoms of Depression (14 Cases)

	Insomnia	Appetite	Mood	Retardation	Agitation
Improved	7	4	9	9	3
No Change	6	9	4	4	8
Severity Increased	1	1	1	1	3

date did not remain with the patient longer than 30 minutes after the injection. The maximum total daily oral dose was 360 mg. and the maximum single intravenous dose was 40 mg. The total dosages of methylphenidate ranged from 60 mg. to 360 mg. daily with an average dosage of 260 mg. daily. Ten of the patients were also receiving phenothiazine drugs for their tranquilizing effects, and two were on imipramine hydrochloride, an antidepressant. Barbiturates were permitted for sleep on a prn basis in all instances.

Results

A. The results on the combined oral and intravenous methylphenidate can be noted in Table I.

Of the 14 patients, seven had improved sleep patterns with decreased requests for h.s. barbiturates, and in only one instance was insomnia increased. Nine patients showed improvement in mood and decrease in retardation; they became more outgoing and their ward behavior improved. One patient became more withdrawn on methylphenidate—almost as if the drug provided the necessary energy to accomplish this. Three patients responded with a marked increase in agitation while, on the other hand, three other patients enjoyed a lessening of this symptom.

Blood pressures were recorded twice daily on all patients. There was no change in 13 patients. In one instance a hypertensive patient had a decreased average systolic blood pressure of 20 points and a decrease of 10 points diastolic pressure. Eight patients had a weight loss (averaging 4.5 pounds) while on methylphenidate. Four patients had no change in weight, and two patients gained weight, averaging 3.5 pounds. Pulse rates, recorded twice daily, showed no change. In all cases receiving intravenous methylphenidate there was temporary tachycardia and tachypnea lasting from 30 to 60 minutes. None of the patients had any toxic effects on daily oral dosages of less than 320 mg. or with single intravenous injections up to 30 mg. One patient had extrasystoles on 40 mg. intravenously, and one patient developed a severe tremor of the hands when given a daily oral dose of 360 mg.

TABLE II

Diagnoses	No.	Favorable Response	Unfavorable Response*	Emotional Release	Enhanced Psychother.	Side Reactions†
Manic-Deprs. Depressed	2	0	1	2	0	0
Reactive Depression	3	3	0	3	3	0
Involutional Depression	2	0	0	0	0	0
Depression with Schizophrenia	5	4	1	4	2	1
Totals	12	7	2	9	5	1

Dosage I.V.: 20 mg. or 30 mg. once or twice daily.

* 1 Manic-Depressive became acutely paranoid.
1 Schizophrenic developed rapid, acute psychotic episode with severe depersonalization.

† 1 patient developed tachypnea with mild carpopedal spasm and urticaria after repeated I.V.'s b.i.d.

B. The results of the intravenous methylphenidate injections are considered in Table II. These will be discussed separately as there was a difference in the effects of oral and intravenous methylphenidate.

Of the 12 patients who received intravenous methylphenidate, seven patients had a favorable response—meaning they had a marked relief from their depressed feeling and they became better subjects for socializing therapy on the ward. However, the duration of this effect was brief. Relief from depression lasted two hours after the first intravenous dosage but gradually decreased to about 30 minutes after they had received multiple intravenous injections on a b.i.d. schedule. Two patients demonstrated unfavorable psychiatric responses to the intravenous route, i.e., one had a brief but severe depersonalization and one patient became markedly paranoid. Nine of the 12 patients had definite emotional catharsis following intravenous methylphenidate. In each case, this was most marked after the initial injections and tended to diminish as the injections were continued. In addition to the emotional catharsis, considering interviews unrelated to the time of the injections, the

intravenous route enhanced psychotherapy in five of the patients in that they gained hope after having experienced a relief of their depression. Only one of the 12 patients exhibited an untoward physiological side-reaction. This patient developed severe tachypnea with mild carpopedal spasm following the injection. After repeated injections the same patient developed a generalized urticaria and the drug was discontinued. However, almost all patients mentioned a minor, vague light-headed sensation for 60-90 minutes following an intravenous injection. Transient nausea appeared immediately after injection in three cases.

Two patients of the reactive depression group responded so well to intravenous methylphenidate that it was considered a major aid to their recovery. In six of the remaining 12 cases, the drug facilitated psychotherapy and milieu therapy.

Comments

1. Methylphenidate was found to be useful in oral dosages much higher than had been previously published in the literature. In our small series it seemed safe up to 320 mg. daily.

2. Why the patients showed improved sleep patterns in seven instances is not known. The authors suspect a certain amount of rebound phenomena in that discontinuing a CNS stimulant taken during the day might produce a reactive drowsiness at night.

3. Oral methylphenidate, even in the highest dosages, did not nearly attain the degree of symptomatic relief achieved with the intravenous form. The duration of action was similarly short, and empirically seemed to require dosage repetition, every two hours for a reasonable sustaining effect.

4. Methylphenidate has a place in our armamentarium as a symptomatic treatment, an adjunctive treatment, and in some cases a definitive treatment, of depressive reactions of many types. At times it might serve as a useful stop-gap procedure while attitudinal barriers to EST are being removed. At other times it might furnish the necessary motivational stimulus to convince the patient or his family that effective treatments are available and that hospitalization can be accepted. Again, before some other definitive treatment plan has had time to become effective, transient lifting of the depression with intravenous methylphenidate is indicated to facilitate some particular clinical or nursing procedure.

5. In no way do we consider methylphenidate a disease-specific treatment but we see it as a useful CNS-stimulating drug, that is capable of counteracting the symptoms of depression or retardation as part of the total picture in many diagnostic categories.

Summary

The literature and pharmacology of methylphenidate as an analeptic are briefly summarized. Little work in high dosages had previously been reported and an attempt was made to determine its efficacy under such circumstances. Fourteen hospitalized patients representing a variety of clinical diagnoses, but with depression as a major symptom, were treated with high doses of methylphenidate. It was concluded that methylphenidate in high dosages has a useful albeit limited place in our pharmacologic armamentarium in psychiatry. A marked difference between the effects of intravenous administration versus the effects of oral administration was observed.

Ritalin is the trade name for methylphenidate hydrochloride supplied by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

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Prozine Therapy in Emotionally Disturbed Patients

C. H. CARTER, M.D.

A continuing study of the effectiveness of various psychotherapeutic compounds in the treatment of emotional disorders has been in progress at Sunland Center since 1956.[1-3] The results with Rauwolfia alkaloids, phenothiazine compounds and mephenesin derivatives have been encouraging. These compounds have produced improvement in a large percentage of patients. It has become apparent, in the course of these studies, that there is selective variation in the effectiveness of each of these compounds; the drug of choice is best determined by trials with the individual patient. For institutionalized patients uniformity of medication is desirable and the ultimate goal of our studies has been to arrive at a course of treatment which will offer best results in the majority of patients.

In a previous report,[1] it was noted that a combination of chlorpromazine and mephenesin was more effective than either drug separately in the treatment of spastics. Similarly, Barsa[4,5] has demonstrated the superior effectiveness of chlorpromazine combined with meprobamate, a mephenesin derivative, in the treatment of mentally disturbed patients; and Parks[6] has used Prozine, a combination of promazine and meprobamate, in treating the emotional difficulties of patients who failed to respond to meprobamate alone.

The value of a combined medication must be determined on an individual basis except where a definitely superior medication results from combination and the purpose of the present report is to describe results obtained with Prozine in a group of emotionally disturbed patients.

Details of Study:

Prozine was given to 121 emotionally disturbed, institutionalized patients comprising 76 males and 45 females, varying in age from 8 to 45 years; 74 per cent were under 20 years. In all cases the emotional difficulty was associated with other conditions: brain damage, mental retardation, epilepsy, mongolism, spastic conditions, phenylpyruvic oligophrenia, tuberous sclerosis, albinism, muscular dystrophy and cretinism (see Table I).

From Sunland Training Center at Gainesville, Fla.

TABLE I

Clinical Response to Prozine in Emotionally Disturbed Patients

Classification	No.	Clinical Response Good	Fair	Poor
Brain damage	45	36	7	2
Mentally retarded	32	29	2	1
Epilepsy	12	10	1	1
Mongoloid	10	7	3	0
Spastic	9	9	0	0
Phenylpyruvic oligophrenia	5	5	0	0
Tuberous sclerosis	4	4	0	0
Albinism	2	2	0	0
Muscular dystrophy	1	1	0	0
Cretinism	1	1	0	0
Totals	121	104	13	4
Per cent		86	11	3

The emotional difficulties of these patients were manifest in aberrant forms of behavior including aggressiveness, destructiveness, temper tantrums, crying spells, head banging, self mutilation, masturbation and uncooperativeness.

Of the patients treated 77 had previous tranquilizer therapy (Table II). All other tranquilizers were discontinued but eight patients continued to take their regular anticonvulsants during Prozine therapy. One patient, a cretin, was treated concurrently with thyroid extract. The remaining patients received no other medications. Physiotherapy and psychotherapy, already in progress, were continued throughout the study.

The daily dose of Prozine was determined on an individual basis, depending on the severity of the symptoms and the weight of the patient. Six patients, weighing less than 70 pounds, had one capsule twice a day; 90 patients, one capsule three times a day; 23

took two capsules three times a day; and two had three capsules three times a day.

Before Prozine therapy began each patient was given complete neurologic, psychiatric and physical examination. The behavior pattern of each patient was discussed with attendants and evaluated. The response to Prozine therapy was noted at various intervals, and a final grade was assigned after six to nine months of treatment. The primary criterion was the control of aberrant behavior, although increased neuromuscular control was observed in many cases. The grade was determined according to the following criteria: good, all major behavior difficulties eliminated; fair, some major behavior difficulties eliminated, and response at least as good as that observed with other tranquilizers; poor, no change in behavior, or less control than attained with other tranquilizers.

TABLE II

Comparative Effectiveness of Prozine

Previous Chemotherapy	No.	Effects of Prozine		
		Better	Same	Worse
Chlorpromazine	22	18	4	0
Meprobamate	14	11	2	1*
Reserpine	11	10	1	0
Meprobamate with† benactyzine	5	5	0	0
Hydroxyzine hydrochloride	4	4	0	0
Chlorpromazine and meprobamate with† benactyzine	4	4	0	0
Phenaglycodol	2	1	1‡	0
Perphenazine	2	2	0	0
Chlorpromazine and reserpine	2	1	1	0
Prochlorperazine	1	1	0	0
Trifluoperazine	1	1	0	0
Chlorpromazine and hydroxyzine hydrochloride	1	1	0	0
Chlorpromazine and thiopropazate dihydrochloride	1	1	0	0
Chlorpromazine and meprobamate	1	1	0	0
Meprobamate and reserpine	1	1	0	0
Meprobamate and meprobamate with benactyzine	1	1	0	0
Reserpine and perphenazine	1	1	0	0
Hydroxyzine hydrochloride and meprobamate with benactyzine	1	1	0	0
Hydroxyzine hydrochloride and phenaglycodol	1	0	0	1*
Prochlorperazine and phenobarbital	1	1	0	0
Totals	77	66	9	2
Per cent		86	12	2

*These patients experienced drowsiness during Prozine therapy.

†'And' indicates two separate preparations used concurrently. 'With' indicates a combined medication.

‡This patient's response was poor to both preparations.

Results

Improvement in most patients was apparent within four days but some improved more gradually over a longer period. A change in the general atmosphere of the wards and cottages was apparent. They were less noisy; the number of situations which formerly precipitated acute aberrant behavior episodes was reduced. The attendants found more time to render individual service. Undoubtedly, many patients benefited from these secondary improvements in environmental conditions.

The individual responses to Prozine therapy are summarized in Table I. The group with brain damage included patients with congenital, traumatic and postencephalitic lesions. In each case, the presence of a lesion was confirmed by electroencephalographic tracings; 80 per cent of these patients responded well. In seven cases the response was graded as fair. Five of these patients had been as well controlled with other psychotherapeutic compounds (Table II). The remaining two patients showed no improvement; both were given two capsules three times a day.

There were 32 mentally retarded patients with no demonstrable brain lesions. This group was particularly responsive to Prozine therapy; 91 per cent of this group were markedly improved. They became more cooperative and alert, and began to take a greater interest in their own care. In 20 cases the response was superior to that previously observed with other tranquilizers. Two patients had fair response; one of these had been as well controlled with meprobamate alone. The patient whose response was poor experienced mild drowsiness while taking two capsules three times a day.

Prozine therapy was used in conjunction

with regular anticonvulsants for eight epileptics. An additional four were maintained on Prozine alone. The aberrant behavior of 10 of these patients was well controlled; in one case the response was graded as fair. The remaining patient was unimproved by Prozine therapy; he had previously failed to respond to phenaglycodol. There was no evidence of increased seizure frequency in these patients. Six of the seven patients who had been on other tranquilizers showed superior response with Prozine therapy.

Ten hyperactive, emotionally disturbed mongoloids were included in the series. Emotional disturbance in mongoloids is invariably a result of improper handling. Parental rejection and excessive pressure during training elicit a belligerent response from the child. Once established the resulting abnormal behavior patterns are difficult to reverse. Six of these patients had failed to respond adequately to other tranquilizers; in four cases this was the first attempt at chemotherapy. During Prozine therapy, seven of them showed remarkable improvement. They became alert, affectionate and amenable to proper training. In three cases the response was fair; in two of these patients the response was about the same as previously observed with chlorpromazine.

Cases in which emotional disturbance was associated with spastic conditions responded well to Prozine therapy. These patients showed marked improvement in muscular control. The number of frustrations which formerly precipitated acute emotional response was thus reduced. In many cases it was felt that the emotional control was secondary to the muscular control. The patients were obviously encouraged by their own progress and became more responsive to psychotherapy.

The emotional difficulties were associated with various other conditions in the remaining 13 patients (Table I). In all cases Prozine therapy was singularly effective. Eight of these patients had been treated less successfully with other tranquilizers.

In our series 77 patients had been treated previously with other tranquilizers. The comparative effectiveness of Prozine is recorded in Table II; 86 per cent showed better response when Prozine was used; in another 12 per cent the response was about the same. The two patients whose responses were considered worse, experienced mild drowsiness before a satisfactory therapeutic level of Prozine was reached.

The only side effect noted during the entire study was mild drowsiness in four cases. There was no increased frequency of epileptic seizures.

Discussion

As the study of various compounds proceeded, it became increasingly difficult for a new medication to make any oustanding impact on psychotherapeutic medicine. Comparison with previous medications is inevitable. Prozine made an outstanding showing in our hands. It is apparent, from Table II, that considering the desirability of uniformity of medication, this is the preparation of choice in the treatment of emotionally disturbed institutionalized patients. One could anticipate improvement in 97 per cent of patients during group Prozine therapy (Table I). It should be remembered that the improvement rate in group therapy tends to be somewhat higher than in individual cases, due to the interplay of emotions among the patients.

In attaining optimal response in our patients we have previously used combinations of various psychotherapeutic agents. In the majority of cases the dose of each drug was determined on an individual basis. The proportions of meprobamate and promazine in Prozine appear to be satisfactory for the majority of patients. The lack of serious side effects permits long term therapy.

Summary and Conclusions

1. Prozine was used in the treatment of 121 emotionally disturbed, institutionalized patients. Response was good in 86 per cent; fair, in 11 per cent; and poor, in three per cent.

2. In our series 77 patients had been treated with other tranquilizers. In 86 per cent of these patients response to Prozine

was superior; in an additional 12 per cent the responses were equal.

3. Mild drowsiness was encountered in four cases. In two of these, drowsiness was encountered before a therapeutic level was reached.

4. It is concluded that Prozine is an ideal choice for uniform medication in institutionalized patients.

Author's Note: Prozine® capsules (200 mg. meprobamate and 25 mg. promazine hydrochloride) used in this study were supplied by Wyeth Laboratories, Philadelphia, Pa.

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"I Want the Job Done and Refuse to Accept a Memorandum why it Cannot be Done"

EDMUND BERGLER, M.D.

Thomas Edison posted this sign in his laboratory: "There is no expedient to which a man will not go to avoid the real labor of thinking." From this, one could conclude that what is involved in the refusal to think is the perennial wish to save oneself that disagreeable chore. But a paradox unfolds at this point: people go to great lengths to avoid thinking, marshaling innumerable reasons to prove that a specific job "cannot be done." Thinking in negatives is of course just as tiring as thinking in positives. What accounts for the willingness to expend enormous effort in negative thinking and the embargo on even minimum expenditure on positive thinking?

A patient, owner of a large technical laboratory, was a man of many highly profitable inventive ideas. He followed a simple rule in hiring his technical employees. Having weeded out the "misfits," he would hand every new man three printed cards. On the first was printed the statement used in the title of this study: "If I hand out an assignment, I want the job done—even if thinking hurts—and refuse to accept a memorandum enumerating all the reasons why the job allegedly cannot be done." On the second card was a quotation from "The Sulu Sea Murders," by Van Wyck Mason: "Thinking is cheap, but thinking wrong is expensive." For explanation see card No. 3." The third card stated: "As a matter of fact, in this organization wrong thinking is so expensive for you that you are immediately fired. But remember: your beginning salary and your prospects of promotion work out to double what you could get from any of my competitors. Name your price!"

This man entered treatment because of "unendurable tensions"; he explained these as arising from his subordinates' "stupidity." Despite his "three-card system," despite strong financial inducements, the turnover in his office was staggering. Instead of accepting the fact that genius does not grow on trees, to be plucked and offered for hire by technical employment agencies, instead of acknowledging that limited help is preferable to no help at all, he constantly raved at the inefficiency, stupidity, and failure to use brain-power evinced by his collaborators. He was truly an injustice collector, and masochistically misused the situation.

What interests us in this connection is only one facet of the patients problem. The most infuriating aspect of the situation, to him, was his conclusion that the energy used productively in thinking up reasons to "prove" that a specific job was impossible could, if productively used, suffice to achieve positive and satisfactory results. He claimed, therefore, that "unproductive use of energy" forced him to do all the productive thinking

in his office. He rescued himself from "collapse" by constantly changing his personnel. The trick worked for some time, until a "smartie" he had hired managed to hoist him on his own petard. This employee, mindful of the taboo on excuses for failure to do an assigned job, adopted a new technique in his explanatory memoranda. He listed the allegedly unsurmountable technical difficulties involved in a specific assignment not as such, but as factors already known which could be solved by consulting scientific literature. He would then point out that this literature was not available in the firm's files, and would urge creation of the post of scientific librarian. In the meantime, he would absent himself from the office for days at a time, visiting the libraries. Obviously to poke fun at the quotation on card No. 2, he quoted Samuel Johnson: "Knowledge is of two kinds: to know a thing and to know in what book to find it."

This clever gambit stumped my patient at first; what he did, to reestablish himself as omniscient and hyper-knowledgeable, was to provide some answers—invented on the spur of the moment, but attributed to an authority. After a time, he concluded that the "smartie" was pulling his leg and discharged him.

The irony of the situation was that the patient actually shifted his own inner problem, the need to prove that he had to do everything himself (unconsciously he was copying his own overburdened mother)—to a theoretical enigma: why do people think negatively, not positively?

The answer emerges when one considers the even slightly masochistic child's attitude toward "duty." The latter is not taken as an unavoidable necessity and a cold, hard fact, but as a parental imposition and an act of personal malice. To prove that an "injustice" is really being done to him, every child learns at an early age to assemble a great multitude of "reasons" proving why "it cannot be done." Later in life this attitude (if not unconsciously corrected) is unconsciously shifted to professional duties.

What my patient claimed was probably quite true: the amount of energy used in unproductive thinking would have been sufficient to accomplish the job at hand productively. But the unconscious thinking of injustice collectors—and the average person has at least some traces of the psychic masochistic scourge in him—is not regulated according to mathematical formulae of energy quanta, but according to psychological and unconscious formulae.

Only *after* the older and infantile technique of finding duty an "injustice" is overcome can mature and productive thinking take over—provided "imagination" is not inhibited. But that is another problem. Relatively few people accomplish the unconscious transition from infantile to adult concepts of duty, regardless of their actual state of knowledge.

The "search for genius," so assiduously pursued in the post-sputnik period in our high schools, colleges and universities, will have to take this psychological factor into consideration.

251 Central Park West, New York 24, New York.

Results with Fluphenazine in Anxiety and Tension

RICHARD C. PROCTOR, M.D.

Anxiety is a basic emotional response of man to sources of annoyance such as the necessity of making an important decision, disturbed interpersonal relationships, or any of a variety of other common situations that may induce feelings of apprehension, uncertainly and fear. Anxiety may also be due to internal unresolved unconscious conflicts that are seeking expression. Normally the anxiety is dissipated as the situation which caused it is resolved. If the situation remains, however, and/or the uncertainty is maintained and turned inward by the individual, an anxiety state may be said to be present. If unrelieved, this state may ultimately manifest itself in various physical signs and symptoms for which the individual seeks medical help.

Anxiety states are commonly encountered in present day medical practice, and their treatment comprises an important part of the doctor's activities. This is especially true of the general practitioner. Before the advent of the so-called tranquilizing drugs, the principal measures available to the physician to combat anxiety symptomatically were sympathetic reassurance of the patient and the administration of sedative agents. The tranquilizing drugs, however, with their capacity to calm and to relax the patient without hypnotic effect or inducing confusion of mind, can be of immeasurable help in alleviating symptoms of anxiety, especially when a favorable rapport between physician and patient has been established.

Recently, a new tranquilizing agent known as fluphenazine (Prolixin) became available for clinical trial. This drug had exhibited unusual potency in its tranquilizing action in laboratory animals (1) as well as extremely rapid action in relieving excitement and anxiety in psychotic patients when administered in doses as low as 2.5 mg. to 10 mg. a day.[2-3] Fluphenazine is a trifluoromethyl-hydroxy-ethyl piperazine-propyl derivative of phenothiazine.[1] The powerful tranquilizing action of the drug as well as the rapid relief of anxiety which followed its administration in extremely low doses indicated its potential usefulness in the treatment of patients who are encountered in daily medical practice suffering from anxiety. The present report concerns the results of a trial of fluphenazine in the treatment of patients with anxiety and tension who were referred to this clinic for diagnosis and therapy. As the report shows, fluphenazine provided relief of symptoms of anxiety in the majority of patients treated.

Department of Psychiatry, Bowman Gray School of Medicine, Winston-Salem, N. C.

Fluphenazine used in this study was provided by E. R. Squibb & Sons as Prolixin.

Method of Study

A total of 25 patients displaying a variety of manifestations of anxiety and tension was treated with fluphenazine. Of these, 13 were male and 12 were female, with ages varying from 20 to 62 years. The symptoms of anxiety presented by the patients included such complaints as general nervousness, irritability, insomnia, nightmares, "tension headache" and globus, as well as such signs as trembling, agitation, crying spells excessive sweating and nausea and vomiting. In addition, several of the patients expressed fear of leaving home, dread of crowds, or even apprehension over getting into a car. Symptoms first appeared in the patients from several months to as long as three years before, the study began, and in general were related to emotional strain involving domestic difficulties, job responsibilities, or other types of situational stress. In addition to anxiety, two of the 25 patients presented evidence of psychotic reactions, one having received electroshock therapy for recurrent attacks of mania and the other exhibiting obsessive-compulsive behavior in his frequent repetition of many acts.

Prior to treatment with fluphenazine each patient received a routine physical examination to rule out the presence of organic

disease as a factor in their complaints; the examination included the usual determinations of body weight, blood pressure and pulse rate, a complete blood count and urinalysis and, where indicated, an electrocardiographic examination and chest x-ray. Patients were re-examined at intervals of one to two weeks throughout the period of study. Blood and urine studies were performed in every case after completion of treatment with the drug. Physical findings were normal in all but two cases. In one of these, there was congenital absence of the right pectoral muscle and in the other there were residual effects from a previous attack of poliomyelitis, and the patient walked with two canes. However, in every case there was no apparent organic basis for the complaints for which the patient had sought relief.

Fluphenazine was administered to each patient as a 1 mg. tablet throughout the entire period of therapy. The usual initial dose was 1 mg. twice or three times daily with the high dosage reduced to 1 mg. twice a day as soon as the patient showed signs of improvement. In two cases, however, four tablets of fluphenazine a day were prescribed, though the dose was reduced to two or three tablets a day because of the appearance of side effects. In a third case, the total daily dose was increased to 5 mg. of the drug before relief of symptoms was achieved. Once relief was attained it was maintained by continuing for one month the dosage of 5 mg. a day (which was the highest dose prescribed for any patient) with no apparent reaction of the patient to the drug. In all but seven cases treatment with fluphenazine was continued for from two to six months. In two of these cases the drug was discontinued after one or two days because of side effects and in the other five it was discontinued after two weeks because the patients showed no improvement.

Results

Many obvious difficulties exist in any attempt to evaluate the results of therapy in patients with emotional disorders, principally because of the subjective nature of most of the complaints for which the patient has been treated. For purposes of this study, however, a patient was considered either to have improved or not to have improved following treatment with fluphenazine on the basis of whether or not his symptoms were relieved. For example, a patient was considered to have improved if before treatment he felt nervous, irritable and could not sleep but after treatments he was calm and relaxed and could sleep. On such a basis, 18 of the 25 patients were considered to have benefited from treatment with fluphenazine. Improvement was usually apparent during the first week of treatment and occurred with equal frequency in older and younger subjects. Of the 18 patients who showed improvement, however, 12 were female and only six were male, despite the fact that more males than females were treated. It is doubtful, however, whether a real difference in response to therapy could be ascribed solely to sex in this study because four of the six males who did not respond to fluphenazine presented symptoms of unusual severity and other factors may have been operative in addition to that of sex. In doses of less than 1 mg. per day, fluphenazine appeared to have little therapeutic value while, in doses above 2 mg. a day, side effects developed in a few patients. However, in the majority of patients, initial daily doses of 3 mg. were administered until the patient began to improve; the dose was then reduced to 2 mg. a day, without the appearance of side effects or the loss of the benefits attained with the higher dosage.

Despite the early improvement shown by most of the treated patients, fluphenazine was continued for several weeks or months because symptoms reappeared when the drug was discontinued.

Five patients developed unwanted reactions to fluphenazine, as given in Table I.

The drug was immediately withdrawn from the patient who developed acute dyskinesis, and the condition cleared within 24 hours. Another patient who complained of dizziness and trembling discontinued the medication himself and could not be persuaded to resume it. In the remaining

TABLE I

Unwanted Reaction	No. of Patients* Male	Female	Total	Dosage of Fluphenazine Administered
Acute dyskinesis	1	0	1	1 mg t.i.d.
Dizziness	1	2	3	1 mg t.i.d. or q.i.d.
Trembling	1	0	1	1 mg t.i.d.
Muscular twitching	0	3	3	1 mg t.i.d. or q.i.d.
Drawing sensation	0	1	1	1 mg t.i.d.

*More than one reaction in some patients.

three patients, the side effects disappeared promptly after a reduction in the dosage.

Laboratory studies at the end of the treatment period revealed no change in the blood and urine values.

Discussion

Fluphenazine appears to be a potent tranquilizing drug which when given in the proper dosage will provide marked therapeutic benefit symptomatically to patients suffering from anxiety and tension. Doses of less than 1 mg. per day are of little or no therapeutic value. The safe dose seems to be 2 mg. a day, since none of the patients in this series developed side effects while on that dosage. Because the slight difference between a therapeutic dose and a dose that may produce side effects, fluphenazine should be administered carefully and watched closely. With one exception—that of acute dyskinesis—all of the side effects observed in this series were uncomfortable rather than dangerous to the patient, and immediately cleared upon reduction of the dosage. Nevertheless, relief of anxiety can be attained and maintained in the majority of patients treated with fluphenazine in doses which will not produce reactions.

As with all tranquilizing drugs, basic personality structure is not changed. Many times psychotherapy of a more formal nature is required. This should not be interpreted to mean that reassurance, emotional support, sympathetic understanding, etc., are forms of psychotherapy. Some patients require more than this, and psychotherapy with "uncovering and reconstruction" is necessary for anxiety that is deep-rooted.

Summary

Twenty-five patients suffering from anxiety and tension have been treated with fluphenazine in daily doses of 2 mg. to 5 mg. for periods of from two weeks to six months. Eighteen of the 25 patients obtained relief from the symptoms and complaints for which they had sought treatment. Improvement was usually apparent during the first week of therapy and occurred in older individuals as frequently as in the younger patients. More females than males improved, though there is considerable question whether the improvement could be related solely to a sex difference because of other factors present. Despite early relief of anxiety, treatment was continued in those who improved to prevent the recurrence of symptoms. Seven of the 25 patients did not improve during treatment. In two of the seven, the drug was discontinued because of side effects; in the remaining five, treatment was withdrawn after two weeks without apparent relief.

Five patients developed unwanted reactions to the drug, these being dyskinesis, dizziness, trembling muscular twitching and a "drawing sensation." Treatment was discontinued in the patient with dyskinesis because of the acute nature of the reaction. Another patient who developed dizziness and trembling discontinued the drug himself and refused to resume it. With a reduction in dosage, the side effects in the other three patients disappeared promptly.

Results of this trial indicate that fluphenazine is a potent and useful tranquilizing drug which when given in the proper dosage will provide marked symptomatic relief of anxiety and tension in ambulant patients encountered in daily medical practice. Because the drug is so potent, it should be administered to patients under the careful supervision of the physician to minimize the occurrence of unwanted reactions. Such reactions usually disappear following a reduction in the dosage or withdrawal of the drug.

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A "Browsing" Double Blind Study of Iproniazid in Geriatric Patients

A. K. SHAPIRO, M.D., K. T. DUSSIK, M.D., J. C. TOLENTINO, M.D., and M. ASEKOFF, M.D.

For several years considerable enthusiasm has been expressed about the use of iproniazid in the treatment of depressed patient.[1] However, to date only one double blind study (on schizophrenic patients) has been reported.[2] Two uncontrolled studies cite an improvement of 65 and 75 per cent in geriatric patients.[3,4] Consequently, although the number of patients evaluated in this double blind study is small, we thought our findings would be of interest.

Sixteen chronically depressed, state-hospitalized, elderly, female patients were chosen for the study. Four were dropped because of illness during the control observation period. Diagnoses included: eight involutional psychotic reactions, two manic depressive reactions and two senile psychoses. All displayed prominent depressive symptoms and had not responded to a variety of treatment methods. The patients were matched and randomly assigned to two groups. There was no significant statistical difference between groups on variables such as age (average 68 years), length of hospitalization (average 5.5 years) and duration of illness (average 15 years). Patients were observed during a control period for one to two months and then placed on iproniazid or placebo (under double blind conditions) and observed for three to five months. The drug was administered in dosages of 25 mg. t.i.d. for one month and increased to 50 mg. t.i.d. if improvement did not occur. The dosage was decreased or omitted if side effects or a worsening of the condition occurred. A vitamin tablet containing pyridoxine was administered throughout the study. Appropriate bi-weekly laboratory procedures were obtained. The patients were evaluated by two psychiatrists and four attendants. A Fergus Falls Inventory was done by attendants.

Only two of the comparisons rated more patients improving on iproniazid than on placebo at a statistically significant level of 5 per cent—psychiatrist B compared with other rators, and the grouped ratings of the two psychiatrists compared with the grouped ratings of the four attendants (see Table I). The Fergus Falls Inventory did not discriminate between groups.

The quality of improvement was marked in one patient who was almost mute, withdrawn and disoriented prior to treatment. After one month on 75 mg. iproniazid daily, and concurrently with increasing the dosage to 150 mg. daily, she became talkative and oriented, worked on the ward and related well to personnel although somewhat hyperactively. The latter was diminished with sedatives which were administered concomitantly with iproniazid. Improvement in the other patients was perceptible but not marked, and involved improved communicativeness, appearance, ability to sleep, appetite, general habitus and weight gain. However, some of the patients on placebo manifested similar changes.

TABLE I

Clinical Evaluation

Drug	Evaluation	Psychiatrists		Attendants			
		A	B	A	B	C	D
Placebo	Improved	2	0	0	2	2	2
	No Change	2	6	4	3	3	2
	Worse	2	0	2	1	1	2
Iproniazid	Improved	4	5	1	1	1	5
	No Change	2	0	2	3	1	1
	Worse	0	1	3	2	4	0
		NS	*	NS	NS	NS	NS
			*			*	

*Statistically significant at the 5% level of confidence.
NS—Not statistically significant.

From Massachusetts Mental Health Center, Boston Psychopathic Hospital, Harvard Medical School and Metropolitan State Hospital.

Iproniazid, the generic name for Marsilid, and the placebo tablets were supplied through the courtesy of Hoffmann-La Roche Inc., Nutley, N. J.

Pre- and post-study attitudes about the drug's effectiveness were compared. Two psychiatrists and one attendant, who rated more patients improving on iproniazid than on placebo, considered the drug more effective post-study compared to pre-study. The opposite direction is noted in the three attendants who rated more patients improving on placebo. Prior to revealing the double blind code, all the rators predicted which patients were thought to be on iproniazid or placebo. The psychiatrists assigned patients to the correct group at a statistically significant level of 5 per cent (100% and 92% correct) while there was no significant difference in the assignment among the four attendants (75%, 55%, 50% and 25% correct). Thus, there is a tendency for correlation between the evaluation of improvement, post-study attitudes about the drug's effectiveness and the ability to predict whether patients were on drug or placebo. We will not go into the various interpretations of this data except to mention the possibility of the psychiatrists not being objective because the double blind procedure broke down (as suggested by the correct prediction).

Three iproniazid patients developed hypotension, dizziness and unsteadiness. This was considered serious in this group of elderly patients because of the possibility of fatal fractures and cerebrovascular thromboses. Two patients fell, one requiring sutures for a chin laceration, and a third had to be put to bed. These side effects occurred during the second month concurrent with the increased dosage and responded to reduction of the dosage to 50-75 mg. per day. A third patient developed sore, dry gums in the third month. However, three patients on placebo had side effects: One complained of burning and sweating. Two patients developed very abnormal thymol turbidity values of 14 and 15, five being the upper limits of normal. This certainly would have been attributed to iproniazid had the patients been on the drug. It again points to the importance of placebo controls in clinical studies to minimize the exaggerated reporting of side effects.

It might appear that the double blind method broke down because of the successful prediction. This, however, does not in itself destroy the usefulness of a study or of the double blind method. This might be the result of a drug's successful action compared to a placebo. In this study, for example, two of the patients, without side effects, who were thought to have shown the most improvement, were placed in the iproniazid group because of the improvement. This methodological difficulty should be considered, nevertheless, by including, whenever possible, an active control substance with effects simulating the side effects of the experimental drug, and/or by counteracting the side effects of the experimental drug.

The considerable variability among the rator's evaluation of change indicates that improvement was minimal. If iproniazid had resulted in dramatic changes, ratings would have been less variable. Complete cure or discharge is an inadequate criterion, however, because of the very poor prognoses of these patients.

Despite the latter, the small numbers in this series and other shortcomings in the study, we felt that we came closer to a reliable evaluation of the drug than if we had conducted an uncontrolled study. Our tentative conclusion is that more patients demonstrated some improvement on iproniazid than on placebo.

A. K. Shapiro, N. Y. U.-Bellevue Medical Center, 550 1st Ave., N. Y. 16, N. Y.

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Trifluoperazine, a Potent Tranquilizer

RAFAEL TROYANO-RIOS, M.D., and JOHN L. SIMON, M.D.

Trifluoperazine ("Stelazine," S.K.F.), one of the more recently developed phenothiazine derivatives contains (as may be seen from its formula of 10-[3-(1-methyl-4-piperazinyl) - propyl] - 2-trifluoromethyl phenothiazine), the substitutions upon the promazine structure found in prochlorperazine ("Compazine," S.K.F.) and trifluopromazine ("Vesprin," Squibb). We have recently had the opportunity to test this new addition to the group of phenothiazine tranquilizers.

Since both prochlorperazine and trifluopromazine are effective in lower doses than either promazine or chlorpromazine, it might be expected that the new drug, trifluoperazine, would be effective in smaller doses than any of these. Such, indeed, had been found to be the case by those who had tested the drug for the manufacturer before it was supplied to us.[1]

Our own observations were made upon 19 patients housed generally in the "B" Building at the State Psychiatric Hospital in Rio Piedras. Of these, ten were males and nine females. The ages ranged from 17 (two cases) to 60, with the mean about 32. The cases were more or less equally divided between acute and chronic.

Our main approach to the use of the drug was to compare its tranquilizing effects with those of earlier preparations. We were also concerned with any toxic effects that might result from its use, and with the extrapyramidal symptoms that the patients might exhibit. Our study was not directed to demonstrate any long-term therapeutic effects of trifluoperazine.

Because of the potency of trifluoperazine as compared with earlier phenothiazines, the doses employed by us were relatively small. In accordance with its sustained effect, we gave the drug but twice daily. We began with doses as small as 5 mg. twice a day. The highest dose we reached was about four times this, or two doses of 25 mg. and 20 mg., making for an aggregate of 45 mg. within the twenty-four hour period. We found the drug to be effective in these small doses. The general tranquilizing effect was comparable to that of chlorpromazine and other previously used tranquilizers. Our experience suggests that the ratio between the effective dose of trifluoperazine and chlorpromazine is somewhere between 1:25 and 1:75.

We also confirmed that the drug is long acting. In one case, a number of days elapsed after the drug was stopped before the side effects produced disappeared. The highest dose given to this patient was 10 mg. twice daily. At the same time we found a significant incidence of concomitant effects of the drug. There was a relatively high occurrence of extrapyramidal syndromes. Eight of our 19 cases had rigidity or tremor or both; one of these may perhaps be discounted since she had only lip tremor.

Sialorrhea, broadly taken to include the emission of a dependent string of saliva from the mouth, occurred in four of our 19 cases. One of us (J. L. S.) has previously described this phenomenon in connection with perphenazine.[2] The picture with trifluoperazine was almost equally striking. While more or less the same can be produced with the older, less potent ataractics such as chlorpromazine, it is less conspicuous than with these newer more highly charged phenothiazines.

Two cases presented vomiting. One of these, nevertheless, was kept on the drug until it was discontinued because of his sialorrhea and extrapyramidal symptoms. He never had more than 10 mg. twice daily. The other case of vomiting, a 42 year old woman, had previously manifested sensitivity to chlorpromazine. She was given only 5 mg. of trifluoperazine twice daily for three days. In addition to vomiting, she presented an allergic reaction of the skin, headache, and vertigo.

Favorable results include the rather difficult to evaluate fact that in one chronic pa-

From State Psychiatric Hospital, Rio Piedras, Puerto Rico.

tient, echolalia disappeared for eight days with trifluoperazine, only to return even though treatment continued. After the drug was released for general use it was employed by a number of physicians on our staff. Their experience confirmed our general impression of the effectiveness of the drug and of the incidence of side effects, especially extrapyramidal, that it produced.

In summary, we were able to conclude that trifluoperazine is by far the most potent phenothiazine tranquilizer to have reached us to date. The margin between therapeutic doses and doses capable of producing marked neurological side effects is very narrow. Patients rapidly develop extrapyramidal symptoms with it. It requires closer medical supervision than does, for example, chlorpromazine. Its very novelty (as, of course, that of any new drug) must in itself be regarded a conditional disadvantage where trained personnel is in short supply. Definite advantages over chlorpromazine were not demonstrated in our limited study.

Trifluoperazine for this study was generously donated by the Smith Kline & French Laboratories, Philadelphia, Pennsylvania.

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Psychiatric Treatment in a State Hospital

JAMES S. TARWATER, M.D.

Psychiatric treatment in a state hospital is much the same as treatment by a private psychiatrist or a psychiatric unit in a general hospital. In treatment outside state hospitals there is less dislocation of the patient from his job, home and community environment and the commitment and forcible admission to a state hospital is avoided. However, there are many who cannot afford private treatment and, by reason of their extremely upset and disturbed states, would not voluntarily accept treatment on an out-patient basis.

With the increasing number of private psychiatrists, general hospital psychiatric units and out-patient clinics, a growing percentage of patients admitted to state hospitals already had some treatment. A large number of admissions have been mentally ill for years and any change in the family constellation may precipitate voluntary admission or commitment. Such a case would usually be referred for longer term treatment in a hospital setting. The state hospital in many states is expected to take in and treat all types from the mentally defective to the organically deteriorated. The majority of patients received by state hospitals are those where rehabilitation and return home is difficult.

State hospitals being in existence for many years, have increased in size to the point where they may house three thousand to six thousand patients, and in some instances even more. A large percentage of the population of any old institution is made up of chronic, regressed patients classifiable in the schizophrenic group. These patients having failed to respond to treatment have gradually accumulated, forming a backlog of so-called chronic and often custodial cases.

As already mentioned, state hospitals are presently admitting many with little chance of release. They, together with the big backlog of chronic schizophrenics, tend to make the function of the hospital twofold: it is a place of intensive treatment, and a place of custody. Therefore the state hospital must provide treatment for the acutely mentally ill patient and also care for the chronic custodial type. It is necessary to provide all types of medical, surgical and dental treatment required by a community of five or six thousand.

I think that treatment in state hospitals

From Bryce Hospital, Tuscaloosa, Ala.
Read at a meeting of the Southern Psychiatric Association, Nashville, Tenn.

is more pleasant and therapeutically rewarding than was true even ten years ago. This change is the result of improvement in our knowledge and use of psychiatry, leading to more freedom and more of an "open door" policy. The first superintendent of the state hospital with which I am connected wrote in his tenth annual report, in October 1870, "'. . . It seems, too, to have been forgotten or discredited in many quarters, that dungeons, cells, chains, cribs shower baths and other appliances of cruelty have long since been abandoned in the scientific treatment of insanity; and that, combined with judicious medication, systematic kindness and undeviating candor, with firmness, are alone the great moral agents upon which the humane and enlightened physician relies for success."

In response to a letter I received in 1953, inquiring about restraints in our hospital museum, I was happy to write:

"This will acknowledge receipt of your letter of March 6th, requesting some of the metal restraints formerly used, but presently stored, in this hospital. It is noted that this material is to be used in casting a Mental Health Bell, the ringing of which will dramatize the launching of the national Mental Health Week observance this year. I am sorry that we cannot participate by furnishing material for this bell, but am happy to state that as far as I know metal restraints have never been used in this institution."

Even though no physical restraint has been condoned in this hospital, there has remained throughout the years a too close and rigid supervision of movement and social environment. We are finding that our patients respond better to the usual therapies such as electroshock therapy, individual and group psychotherapy, and tranquilizing medicines, if they feel that living situations are adequate and that they are allowed some freedom, ground privileges, and opportunities to meet and talk to the volunteer workers and civic and club groups who come to the hospital. We find that a large, active patient program of activities—recreation, occupational therapy and industrial therapy —does much to make a happy and satisfied group. This has been so noticeable that we have wondered how many would walk off if we opened all doors.

With the change in attitude regarding mental illness and state hospitals, patients do not resent commitment and hospitalization as much as formerly. However, we regard admission as a part of treatment and make every effort to acquaint each patient at time of admission that we are interested in his early release. This policy is also part of the early planning with the patients' relatives. This planning concerns ways and means of making a better home situation and better acceptance in the community to insure, as far as possible, against recurrence of symptoms immediately after release.

Formerly there was reluctance to recommend trial at home. The diagnosis of schizophrenia was frightening and the hospital physician was loath to attempt an adjustment outside the hospital. We have had too many hospital adjustments and not enough home and community adjustments. Now we are interested in prompt and intensive treatment of the acute mentally ill with release following as soon as symptoms have subsided and the family and community environment improved sufficiently for acceptance and further care. We are helping arrange aftercare programs in the various counties to take over after a patient returns home, assisting in job placement and furnishing friendly contacts which we hope will lessen the number of "returns from trial visit."

I believe the changes in public attitude, our growing knowledge of psychiatry, and the continued leadership of the great men in the field who have advocated new methods, will bring about further modifications in our treatment in state hospitals. There have already been many changes along lines I have mentioned, and some state hospitals have now found that the large farming operation that was a part of almost every hospital is now outmoded and unnecessary. This operation, while economical and beneficial to the hospital, had taken many patients out of the treatment program. I believe that any industrial therapy program should not utilize the services of a patient for an entire day. He should spend some time in

recreation, occupational therapy and group psychotherapy sessions.

With the new methods and new therapies we have been able to give better reports regarding treatment and release. For the last two or three years there has been a decrease in the number of hospitalized patients. In the hospital with which I am connected we formerly had been accumulating some 75 to 100 patients yearly whereas in 1955 our population declined by 22, and last year for the first time we were able to close the year with a decrease of 17 in our Negro hospital population. This occurred despite the fact that our admission rates were the same or slightly increased over former years.

We are much interested in what can be done for our great backlog of chronic, regressed custodial patients. It is very satisfying to work with this group and see improvement with the newer medicines. We have been invading our so-called chronic sections, selecting those under age forty and moving them into another section of the hospital where they are started on one of the newer drugs, provided with more attendant care, more freedom of movement and as they show improvement placing them into patient activity programs. We are seeing good results.

It appears that it is necessary that state hospitals work on the backlog of the so-called chronic, regressed population to get as many out as possible and to use our best efforts on recent admissions to see that the backlog does not continue to pile up. If we can work toward improving new admissions and getting them back home in a better adjusted state with a better acceptance by the family and community, we may be able to further reduce the state hospital population.

With the broad publicity regarding mental illness spread through magazines, films, television, radio and other media, there may arise this question: Is psychiatry being oversold? Despite help from treatment agencies outside the state hospital, there has been a steadily increasing number of applications for admission in the state hospital of my state, and the number accepted for the first eleven months of this fiscal year is the highest of any year. This fact indicates to me that more families are interested in having something done for their sick or those who might be showing evidence of difficulty in making a harmonious adjustment even though no psychotic state exists.

With more psychiatric units in general hospitals, more private psychiatrists and more out-patient clinics, there should be fewer admissions in state hospitals. Then we may see, as Doctor Harry Solomon has predicted, a need for revamping our hospitals. For this to come about in some hospitals, it will be necessary for the state to provide nursing homes for the feeble, senile and arteriosclerotic patients, the middle-aged mentally defective and other organically deteriorated patients whose needs are strictly custody and care. There are yet a few years, however, in which state hospitals have need for more staff personnel, particularly the younger psychiatrists, most of whom enter private practice after completing their residency training and receiving board certification.

Summary

With the advance of psychiatric knowledge and therapeutic techniques, together with the changed and changing attitudes reflecting better acceptance of psychiatry and state hospitals, hospital personnel are doing a better job.

Working in state hospitals has become more pleasing and therapeutically rewarding with the result that population is tending to decline.

Admission rates in the hospital of my state have steadily increased since 1954 and are today higher than ever before due principally to the interest of the public that more people receive treatment.

With the assistance of agencies outside the state hospital, it is hoped that we can look for fewer admissions of acute cases and for those who can be treated on an outpatient basis.

Eastern Psychiatric Research Association, Inc., Meeting

G. LANGFELDT*

The Philosophy of Albert Schweitzer

On the basis of a study of the works of Albert Schweitzer, Dr. Langfeldt stated that many of the central points of Schweitzer's philosophy of life have been misunderstood. This conclusion was confirmed by a subsequent exchange of correspondence between the two men. For example, several theologians in Norway insisted that Schweitzer still believed in the orthodox God of the Christians. However, with the help of an interchange of letters with Schweitzer, Dr. Langfeldt succeeded in clarifying Schweitzer's beliefs concerning such concepts as that of God, The Figure of Jesus Christ, and The Prayer. Schweitzer not only accepted Dr. Langfeldt's interpretation of his philosophy but gave him permission to state the fact in the preface of a book on the subject which was soon to appear in London.

Among the concepts which were verified by the correspondence are the following: *God* is an historical symbol and, as such, it can have no real content because it is an abstraction. In Dr. Schweitzer's opinion, we can meet God only in *Being*. By acting out love, the "will to live among other wills to live," we fulfill the essential purpose of Life.

The Figure of Jesus, according to Schweitzer, is to be considered not as a real son of God but, rather, as the greatest ethical personality who has ever lived. Christians usually direct *Prayer* to a transcendental God. To Schweitzer, Prayer is an *act of meditation* during which he tries to get contact with the primary eternal source. He feels that this gives us the strength to stay the difficulties of life and helps us to fulfill our high destiny. Schweitzer has never submitted to a single religious dogma. To him, the only thing necessary to fulfill the meaning of life is that "of being man, purely and simply man, in the significance Jesus attached to that" (quoted from Schweitzer's letter of June 10, 1908 to Gustav von Lupke).

As a direct result of holding these concepts, Schweitzer declared himself as an *agnostic* concerning the understanding of what is going on in the world. He does not think that God is responsible for all the misery in the world nor that God is ruling the world. "We lose thereby the comfort which is connected with it," he wrote to Dr. Langfeldt, "on the other hand our religion is getting more purified and strong."

In another part of the lecture, Dr. Langfeldt referred to the personality traits in Albert Schweitzer which had contributed to making him one of the most outstanding personalities of our time. These observations were drawn from a study of Schweitzer's autobiography, "From Childhood to Youth." Dr. Langfeldt stressed that Schweitzer's most characteristic traits were his intellect, his courage, his uncompromising search for the truth and his insistence on rational thinking. In addition, his strength of will enabled him to realize the plan which he formulated at the age of 21. This was to complete his theological, medical and musical studies before he was 30 so that he could devote himself to his purpose of sacrificing himself in the service of humanity. In order to understand this great personality, equal consideration must be given to the mystical forces working in him. Albert Schweitzer has a deeply religious nature with a conception of the mystical forces which, according to his own opinion, places him between deism and pantheism.

In the last part of the lecture, Dr. Langfeldt pointed out the fact that many outstanding thinkers, spread over the whole world, now stress the necessity of a revolution in ethical and religious thinking—away from dogmas. The primary and only necessary command in every religion must be that of practicing love for all human beings. Dr. Langfeldt concluded the lecture by saying that in his opinion, Albert Schweitzer will remain known as a brilliant thinker and a great ethical and religious genius who, by practicing his own ethical principles, has shown mankind the way it must take, if it is to reach its destination. By stressing that ethics are the primary and central factor in people's relations to each other as well as to the great unknown, he has for all time demonstrated the only common principle that is of significance for man's salvation.

Authoritarian Personality and the Obscenity Threshold

WLADIMIR G. ELIASBERG, M.D., PH.D.
and IRVING R. STUART, PH.D.

Many subjects viewing great works of art in the collections of the Metropolitan Museum of Art in New York City report percepts bordering on illusion and hallucination. What they see in these exhibits, in keeping with their primary emotional-moral responses and moral-religious attitudes, is pornography and indecency.

This investigation on the moral effects of great visual art follows an earlier study on the characteristics of true literary pornography. In the present study a student population of 274 men and women (the largest number ever used in an experiment of this nature), had to judge great works of art, i.e., pictures showing single nude females, nude

*Director of The University Psychiatric Clinic, Vinderen, Oslo, and Professor of Psychiatry at The University of Oslo, Norway.

Meeting of Dec. 8, 1959.

women in groups, nude women in company with clothed men and single nude males. Titian, Ingres, Manet, Modigliani and Picasso were among the artists represented. The subjects were asked to write down whether they considered the work pornographic.

The factors that seemed to influence the subjects were the mode and technique of presentation and the personality of the viewer. Sculpture was less "suggestive" because of absence of movement. Photographic realism was more suggestive than paintings. A comparison with the study made of literary works (lecture by W. G. E. before a meeting of the American Psychiatric Association in 1956), showed the reader to be more "innocent" of intended pornography than was the viewer of art in the present study. Monotony, infantilism of expression, cruelty and suffering without any real plot had been found to make up the characteristics of true literary pornography. The same factors, often illusioned, were listed by the subjects as their reasons for considering innocent paintings or sculptures to be pornographic.

The personality factor was measured by the California F Scale developed by Adorno, Frenkel-Brunswick and others in their research of anti-Semitism (*The Authoritarian Personality,* Harper and Brothers, New York, 1950). We found a positive correlation between the F scores and the scores on the pornography scale. The authoritarians are shaped mainly by early childhood experiences. They are often refractory to classroom authority and do not change their judgments once they have evaluated a work of art on a face to face basis. These findings contribute toward an understanding of the circumscribed influence of the critic. Viewers and readers are amenable to the opinion of the critic before having an opportunity to judge for themselves. When they have seen the art, they unconsciously, consciously and aggressively adhere to their ideas, and it is their moral judgment which often presides over what is perceived.

The logical consequence of our findings is an experimental investigation of criticism, and such a study is presently being carried out. In testing pornographic reactions, we gain insight into the relationships of beauty, ugliness, sex, morals, the personality and society. Such testing will help protect for our youth and for society, freedom of thought and expression.

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